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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03102379.9

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Offic

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 03102379.9
Demande no:

Anmeldetag:
Date of filing: 31.07.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Angiotensin II receptor blocker derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D257/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR LI

(NP 0012)

TITLE OF THE INVENTION

"ANGIOTENSIN II RECEPTOR BLOCKER DERIVATIVES"

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The present invention relates to Angiotensin I Receptor Blocker (ARB) derivatives. More particularly, th present invention relates to ARB nitroderivatives pharmaceutical compositions containing them and their us for the treatment of cardiovascular, renal and chroni liver diseases and inflammatory processes.

With the angiotensin II receptor blockers a class o compounds is intended, comprising as main component Losartan, EXP3174, Candesartan, Telmisartan, Valsartan Eprosartan, Irbesartan and Olmesartan Medoxomil.

ARBs are approved only for the treatment o hypertension, the antihypertensive activity is due mainl to selective blockade of AT_1 receptors and the consequen reduced pressor effect of angiotensin II. Angiotensin I stimulates the synthesis and secretion of aldosterone an raises blood pressure via a potent direct vasoconstricto effect.

Now, it has been reported that angiotensin II recepto blockers have side-effects such as for example hypotension, hyperkalaemia, myalgia, respiratory-tract disorders, rena disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia (Martindale, Thirty-third edition, p. 921).

It was now object of the present invention to provid new derivatives of ARBs able not only to eliminate or a least reduce the side effects associated with their paren compounds, but also having an improved pharmacologica activity. It has been so surprisingly found tha angiotensin II receptor blocker nitroderivatives have a significantly improved overall profile as compared t

native compounds both in term of wider pharmacological activity and enhanced tolerability.

In particular, it has been recognized that the angiotensin II receptor blocker nitroderivatives of the present invention can be employed for treating or preventing heart failure, myocardial infarction, ischemic stroke, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and liver fibrosis.

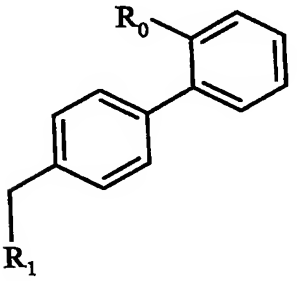
Object of the present invention are, therefore, Angiotensin II Receptor Blocker nitroderivatives of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof:

$$R-(Y-ONO_2)_s \quad (I)$$

wherein:

s is an integer equal to 1 or 2;

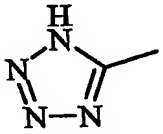
R is selected from the following Angiotensin II Receptor Blocker residues of formula (II) or (III):



(II)

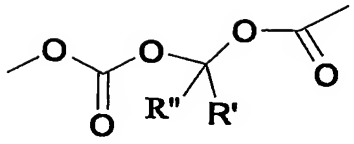
wherein:

R_0 is



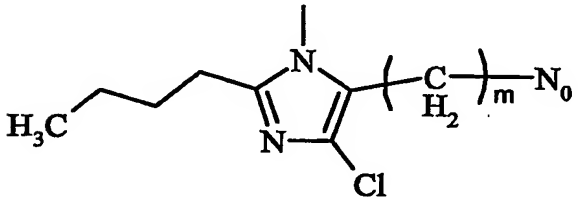
or $-N_0$ which is a group capable to bind to Y, having one of the following meaning:

-COO-, -O-, -CONH-, -OCO-, -OCOO- or

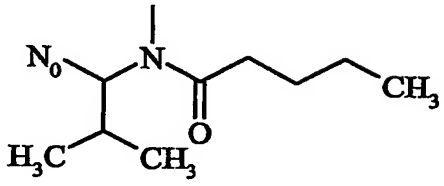


wherein R′ and R′′ are the same or different, and are H or straight or branched C_1-C_4 alkyl;

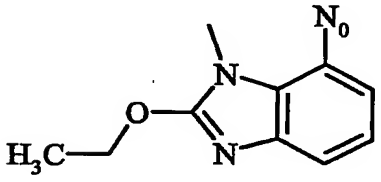
R_1 is selected from the group consisting of:



(IIa)

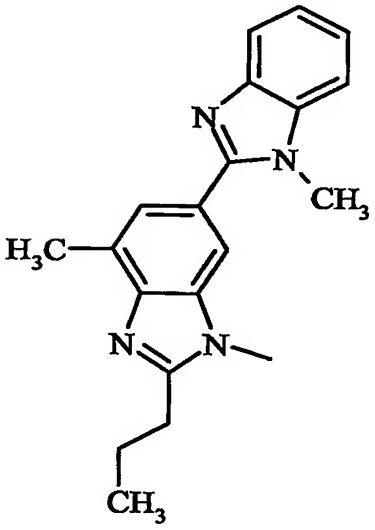


(IIb)



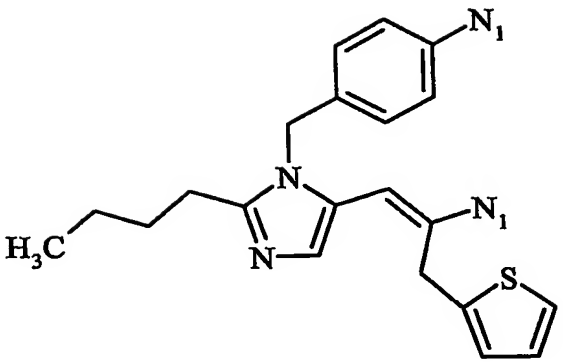
(IIc)

or



(IId)

wherein m is an integer equal to 0 or 1 and N_0 is as above defined;



(III)

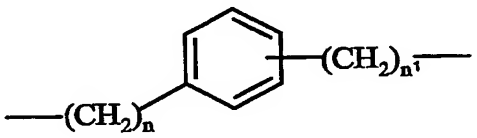
wherein N_1 has the same meaning as N_0 or is equal to -COOH; with the proviso that at least one of the groups N_1 is equal to -COO- or -CONH-, i.e. it is a group capable to bind to Y;

Y is a bivalent radical having the following meaning:

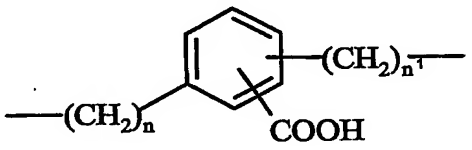
a)

- straight or branched C_1-C_{20} alkylene, preferably having from 1 to 10 carbon atoms;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably CH_3;

b)

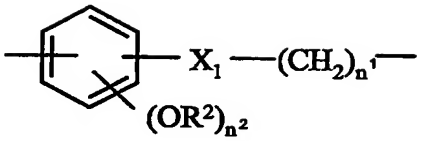


c)



wherein n is an integer from 0 to 20, and n^1 is an integer from 1 to 20;

d)

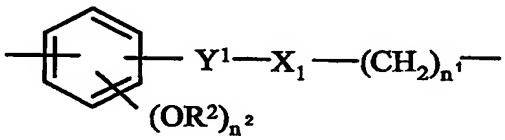


wherein:

n^1 is as defined above and n^2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

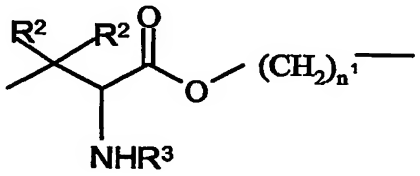


wherein:

n^1, n^2, R^2 and X_1 are as defined above;

Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n^2}-$;

f)

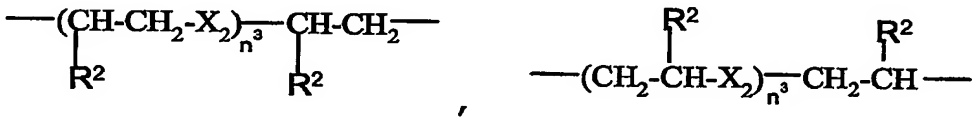


wherein:

n^1 and R^2 are as defined above, R^3 is H or $-COCH_3$;

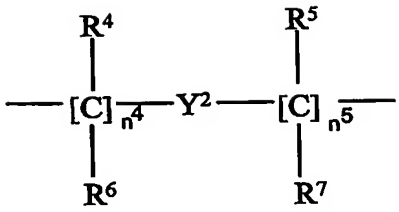
with the proviso that when Y is selected from the bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-CH_2$ group;

g)



wherein X_2 is -O- or -S-, n^3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as defined above;

h)



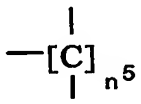
wherein:

n^4 is an integer from 0 to 10;

n^5 is an integer from 1 to 10;

R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^4, R^5, R^6, R^7 are H;

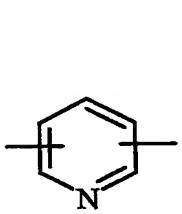
wherein the $-ONO_2$ group is linked to



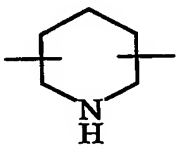
wherein n^5 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

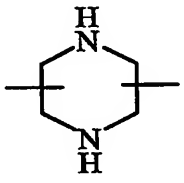
and is selected from



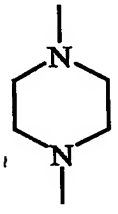
(Y1)



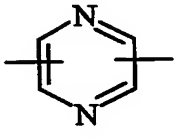
(Y2)



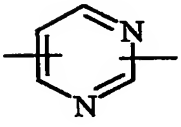
(Y3)



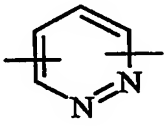
(Y4)



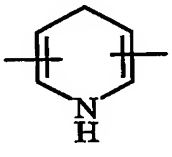
(Y5)



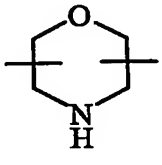
(Y6)



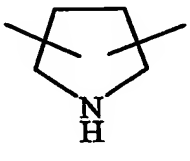
(Y7)



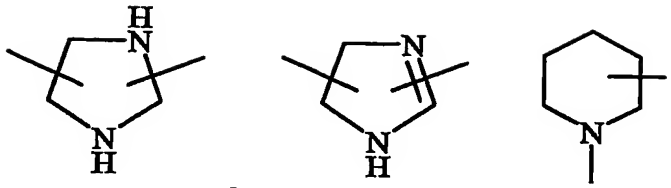
(Y8)



(Y9)



(Y10)



(Y11) (Y12) (Y13)

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

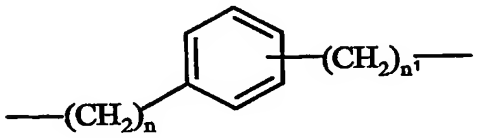
Preferred compounds are those of formula (I) wherein: s and R are as above defined;

Y is a bivalent radical having the following meaning:

a)

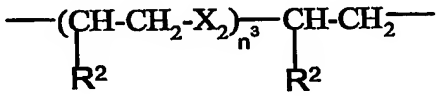
- straight or branched C_1-C_{10} alkylene;

b)



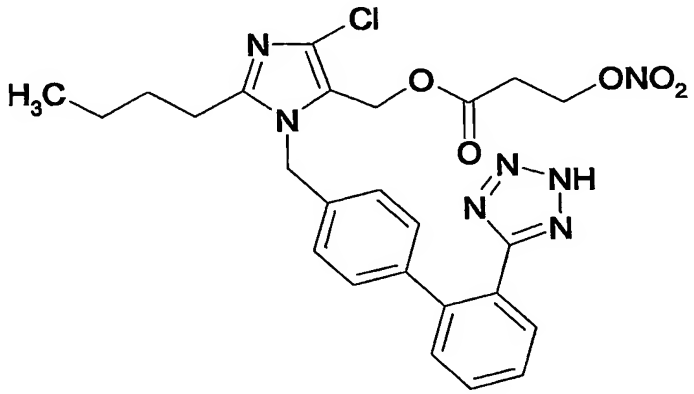
wherein n is an integer equal to 0 or 1, and n^1 is an integer equal to 1; with the proviso the $-ONO_2$ group is linked to a $-CH_2$ group;

g)

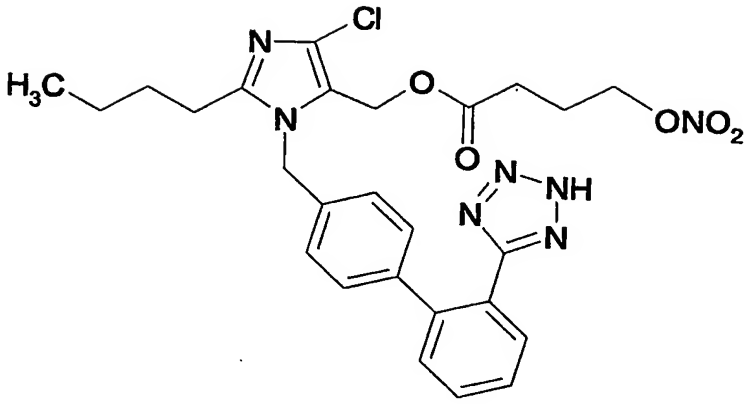


wherein X_2 is -O- or -S-, n^3 is an integer equal to 1 and R^2 is H;

The following are preferred compounds according to the present invention:



(1)



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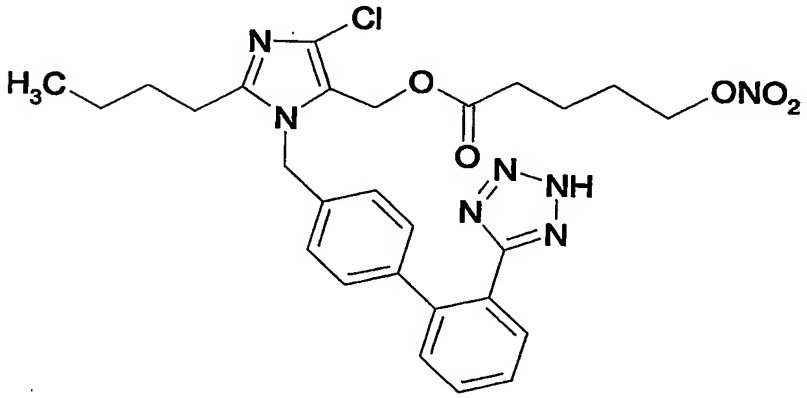

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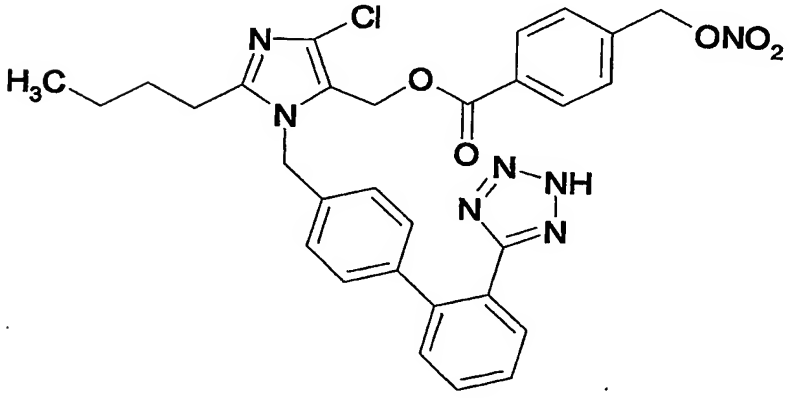

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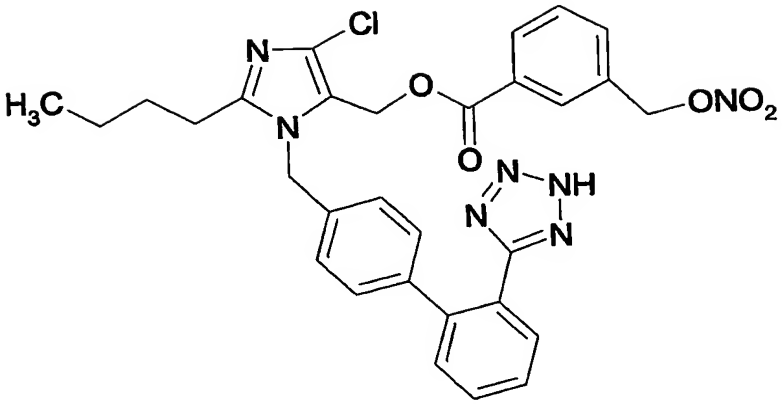

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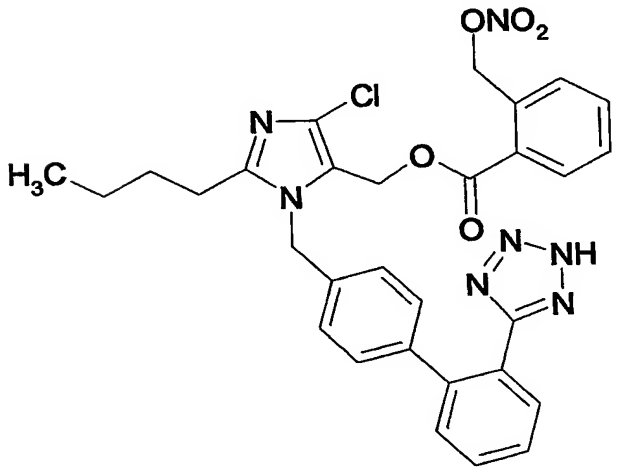

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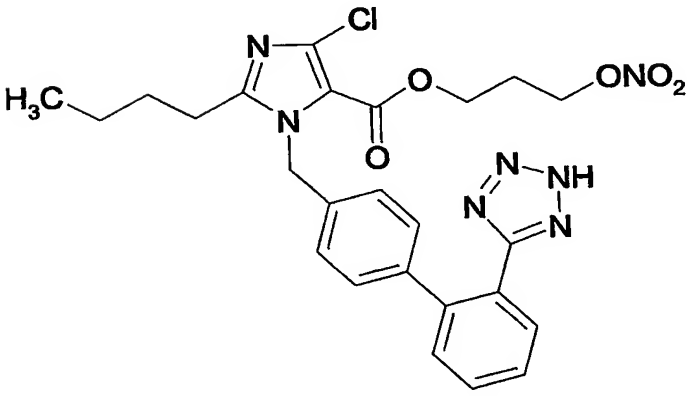

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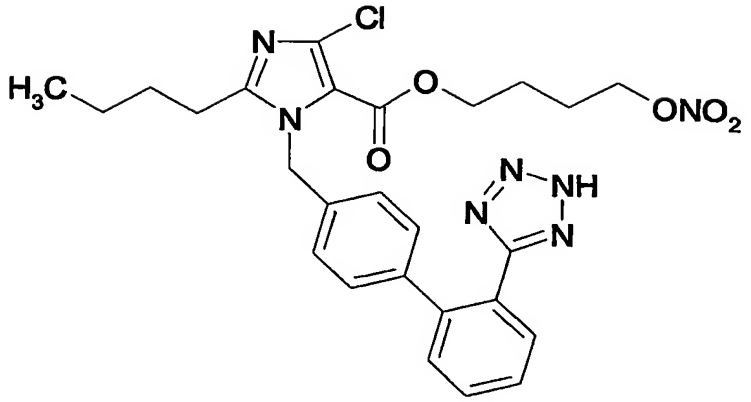

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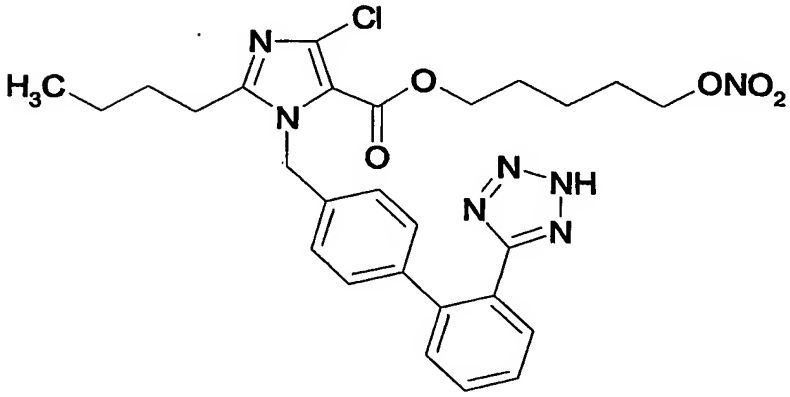

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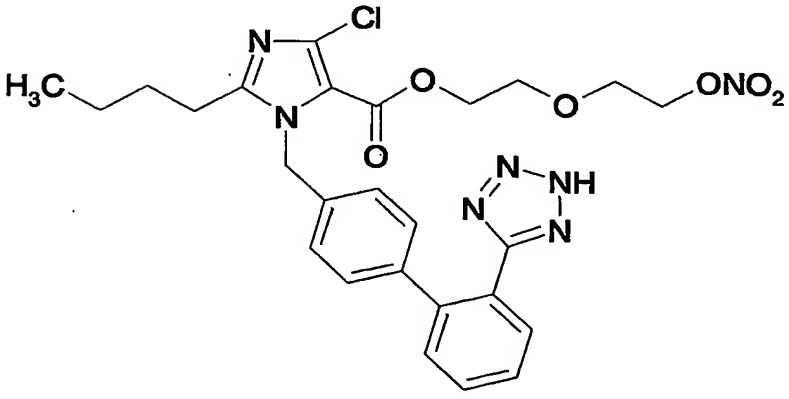

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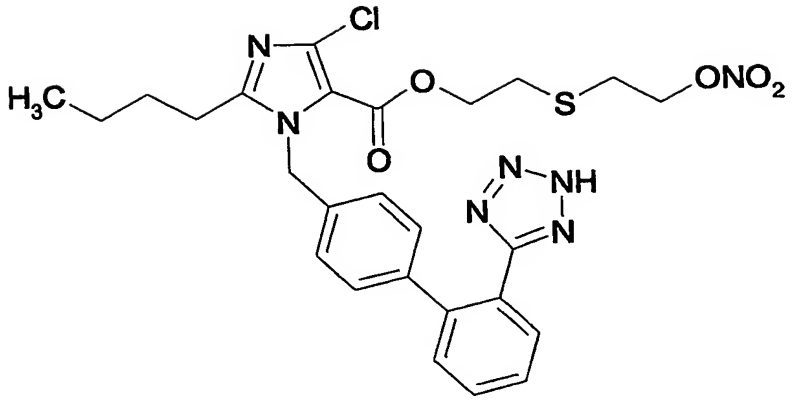

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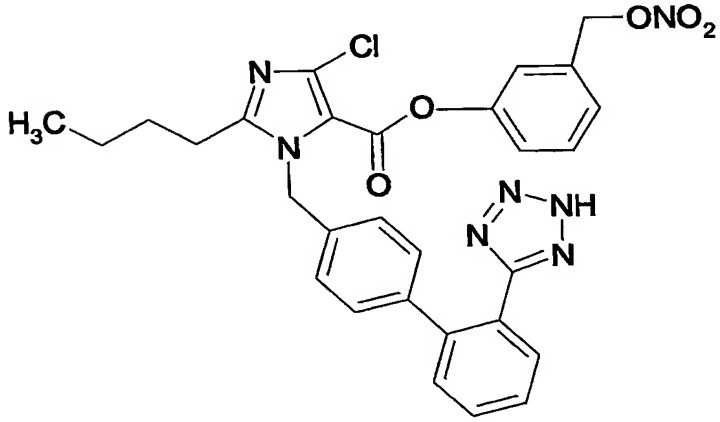

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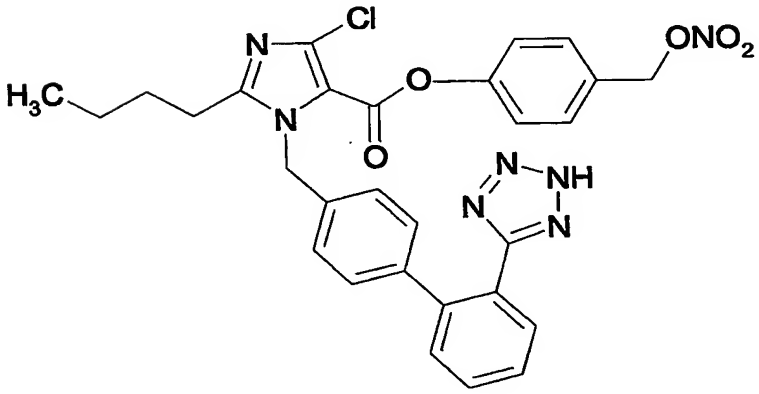

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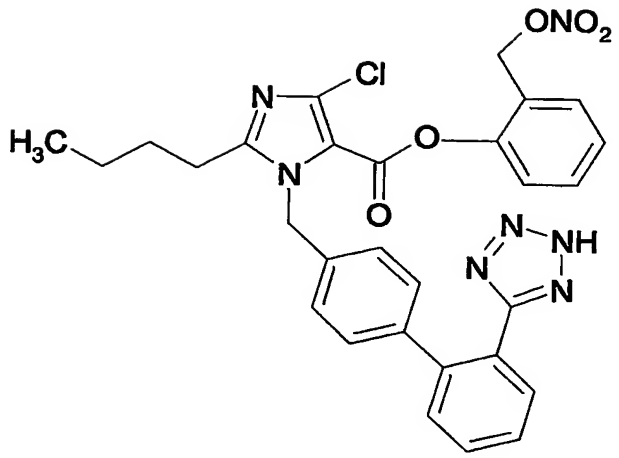

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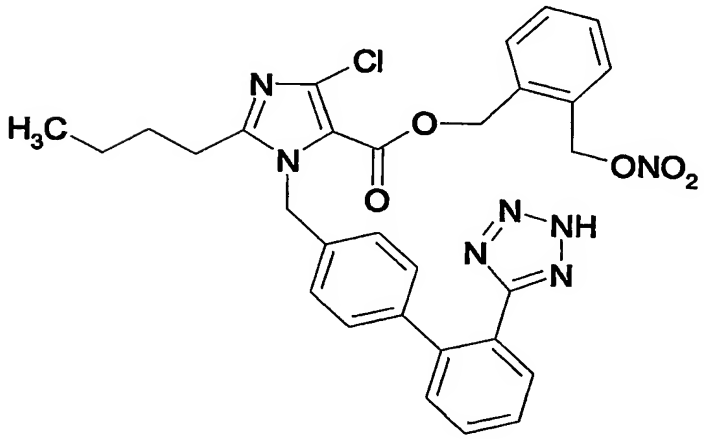

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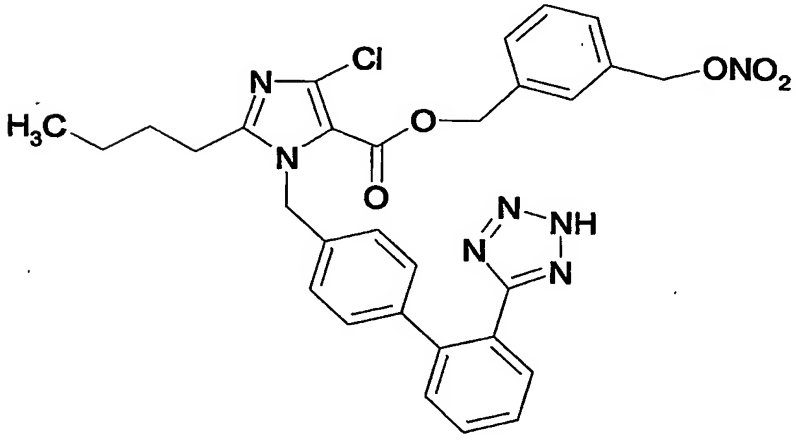

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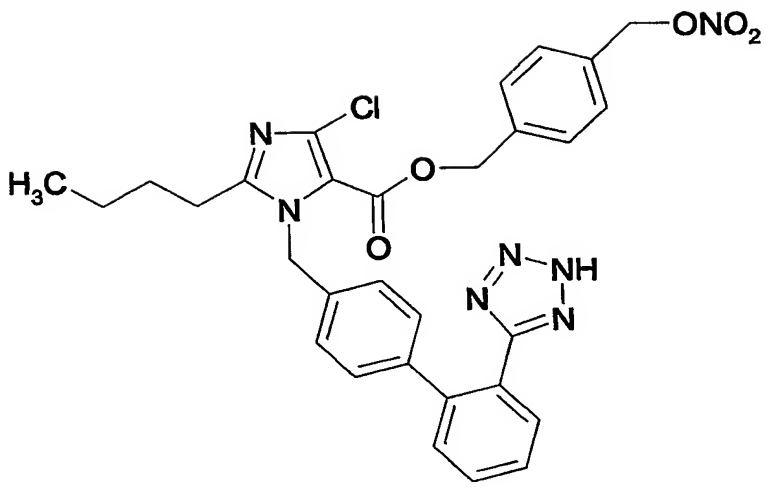

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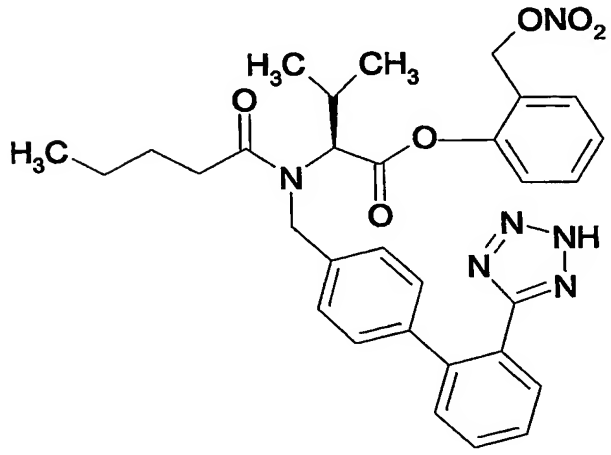

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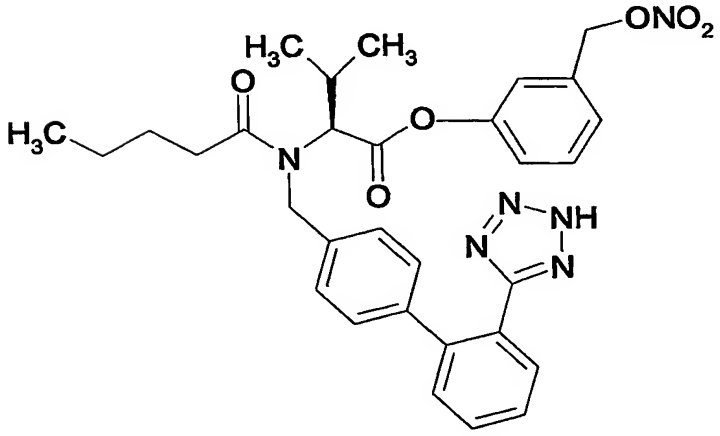

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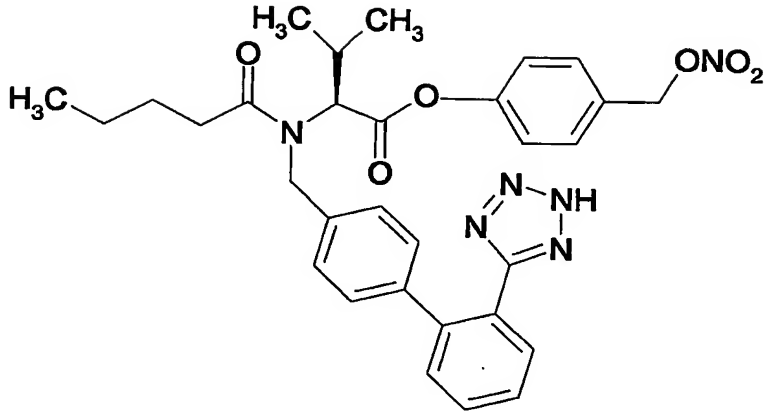

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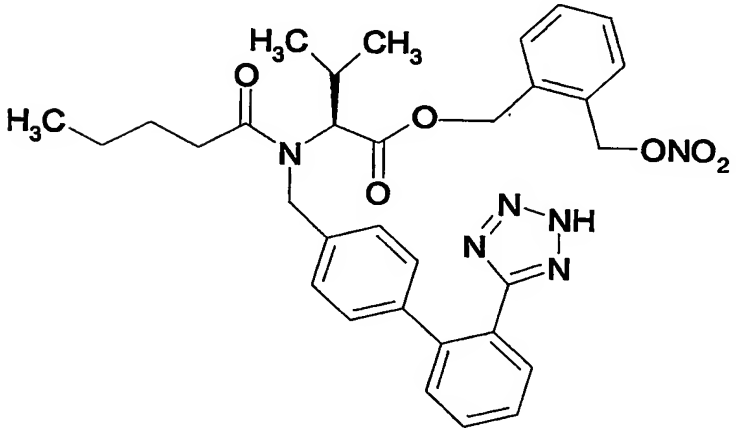

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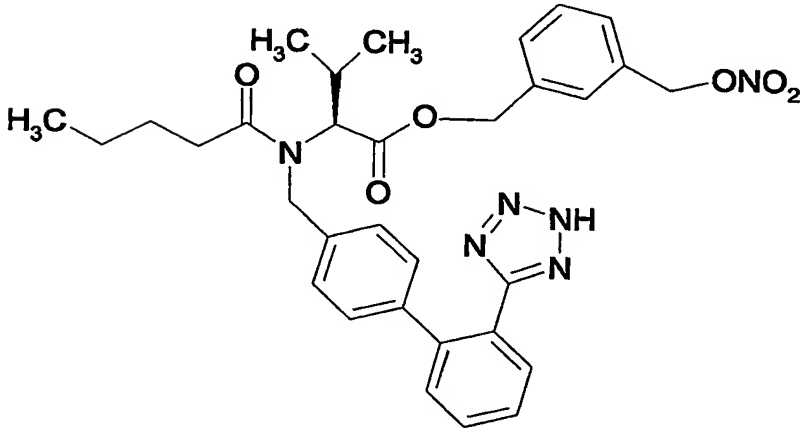

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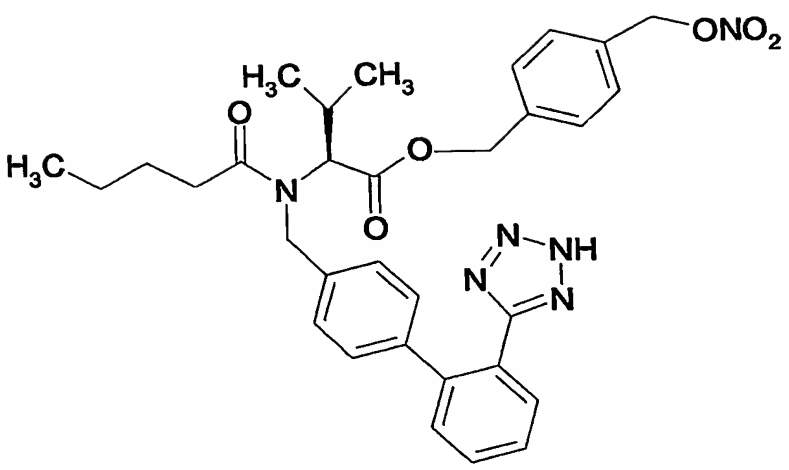

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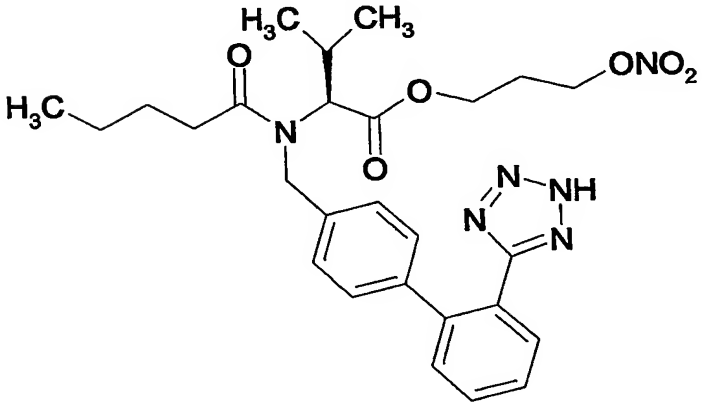

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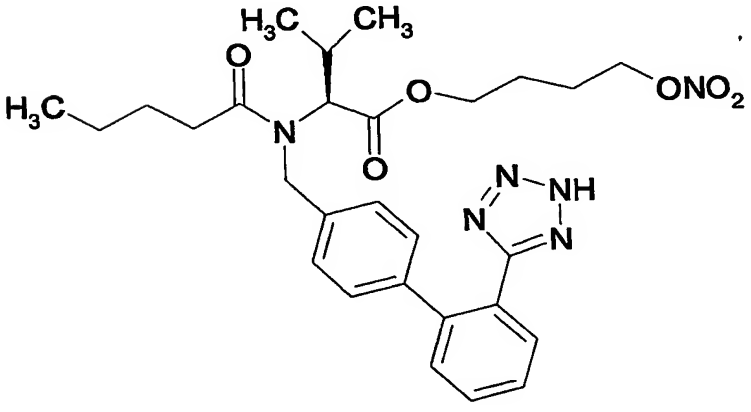

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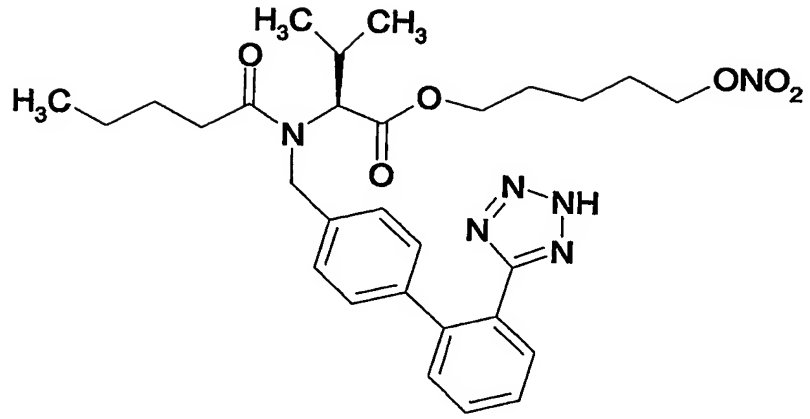

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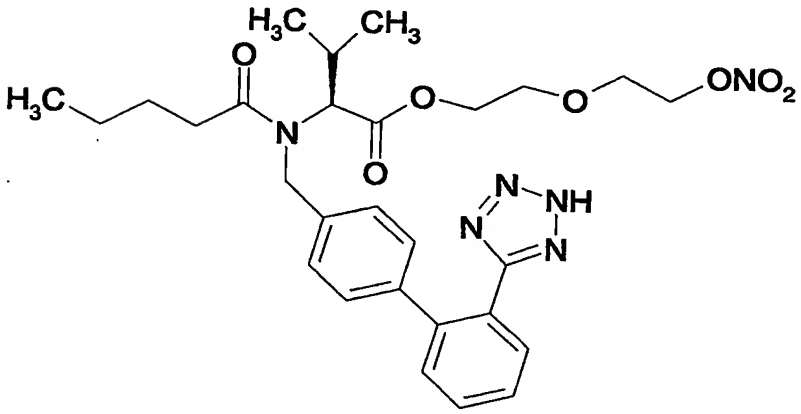

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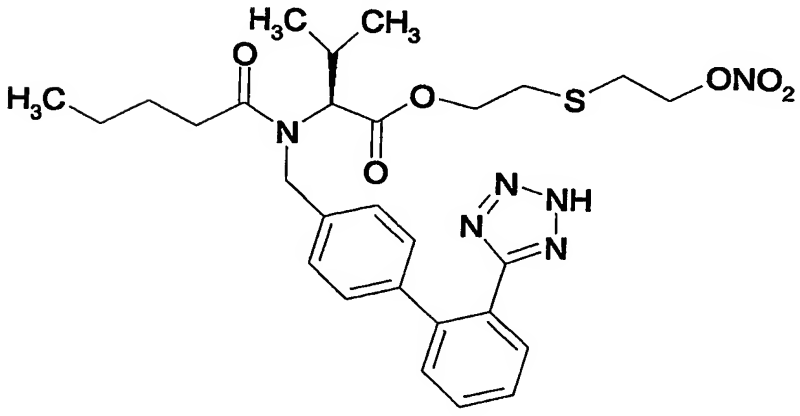

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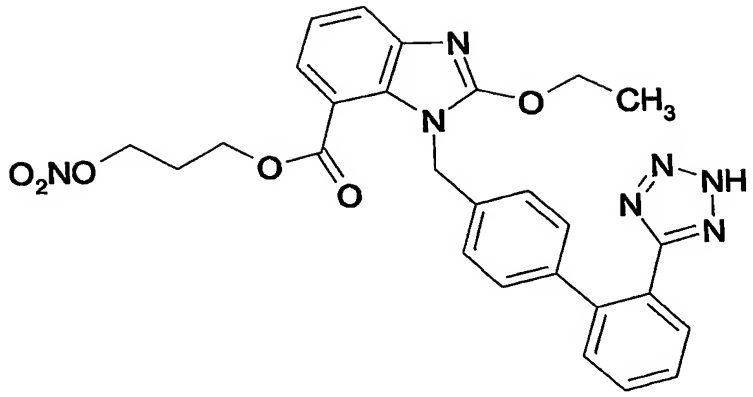

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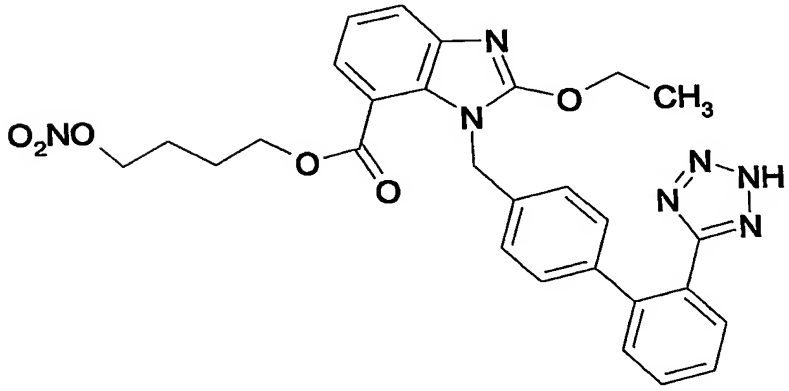

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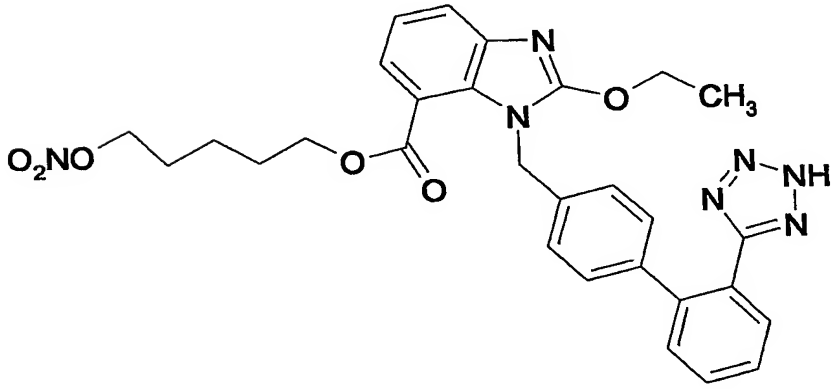

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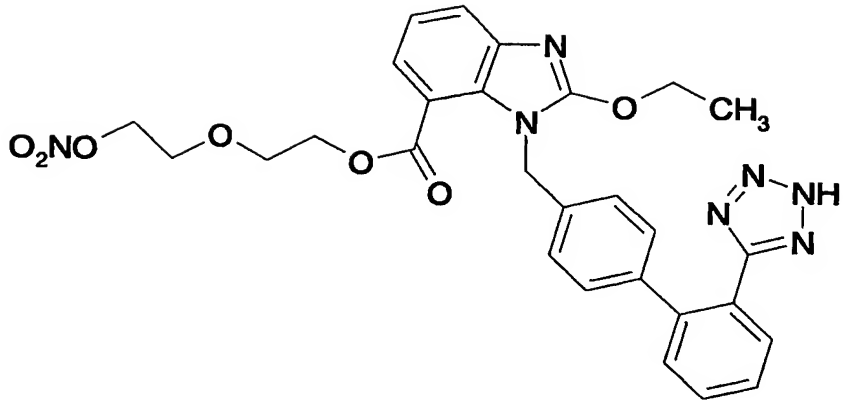

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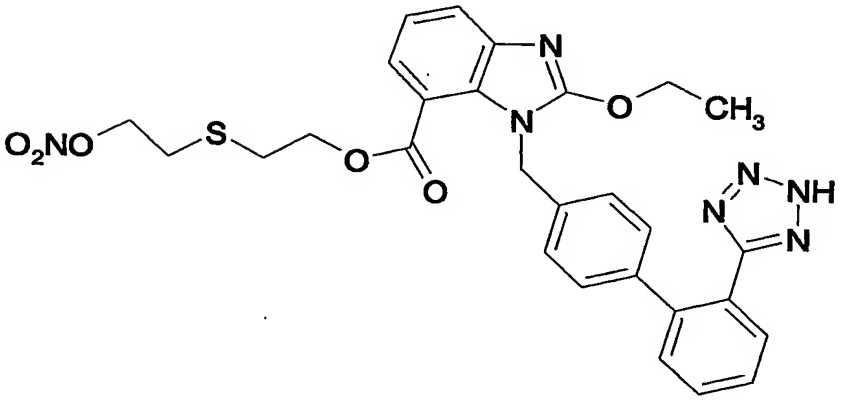

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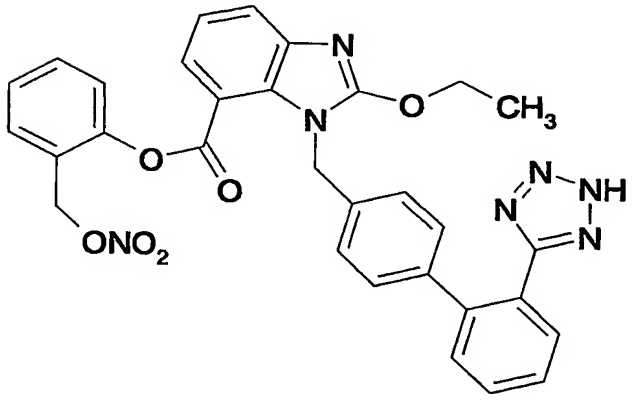

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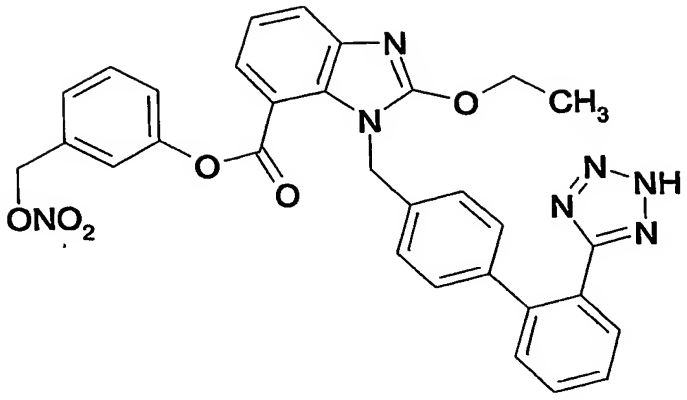

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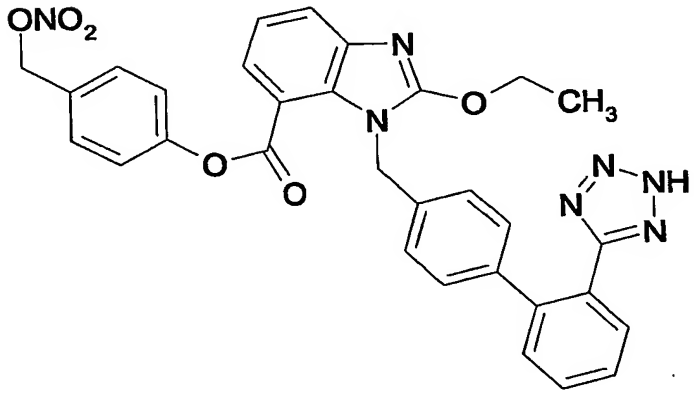

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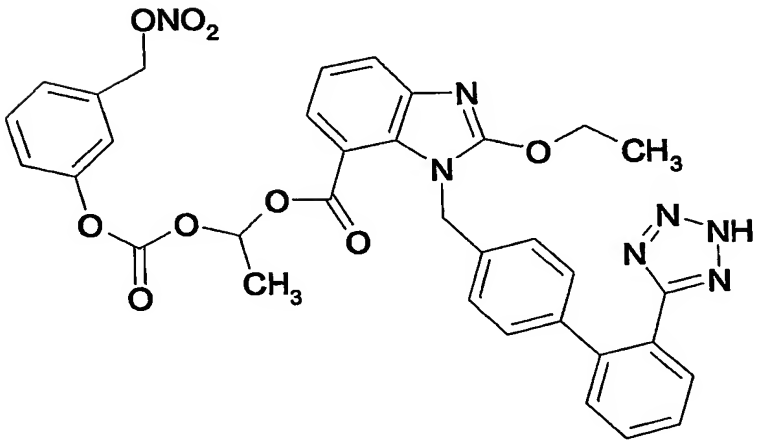

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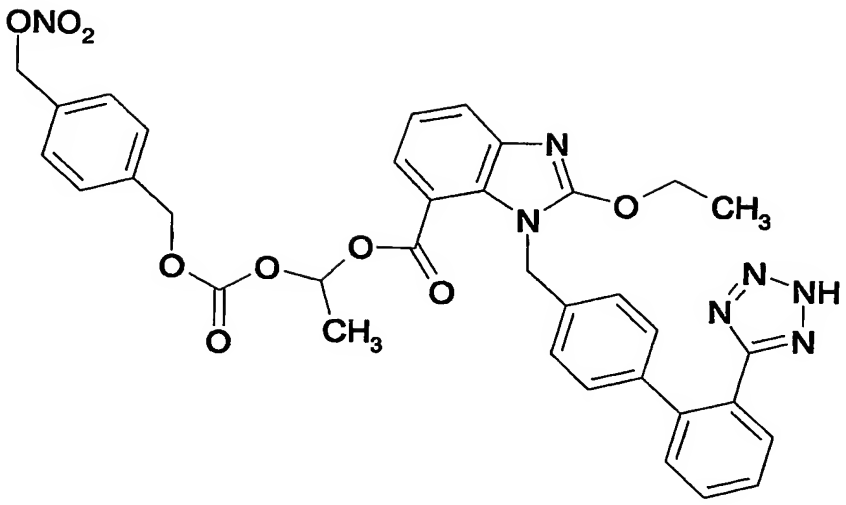

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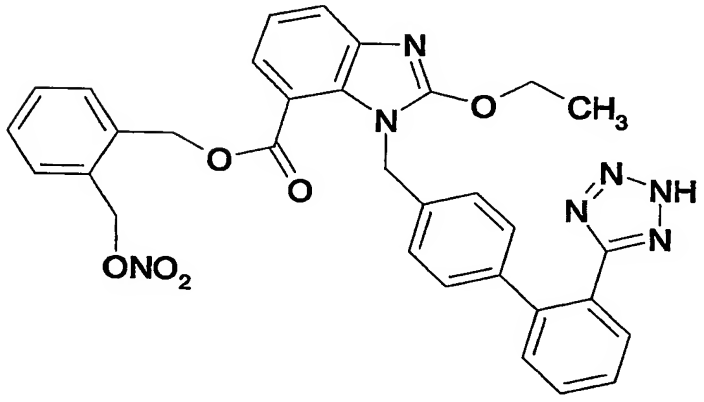

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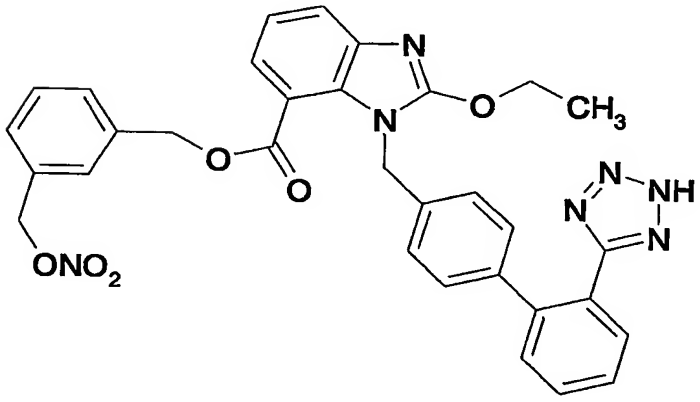

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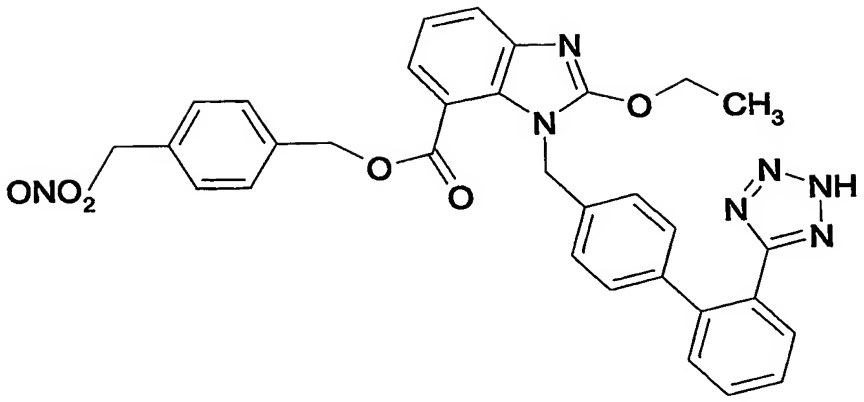

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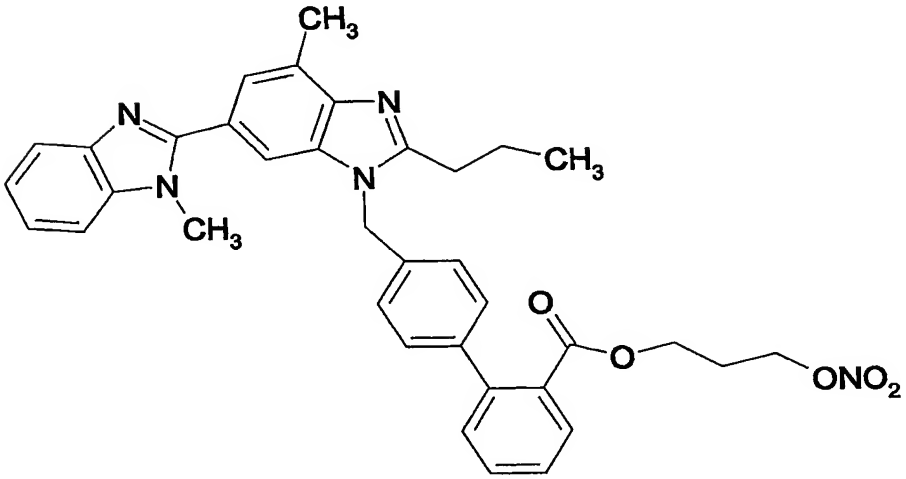

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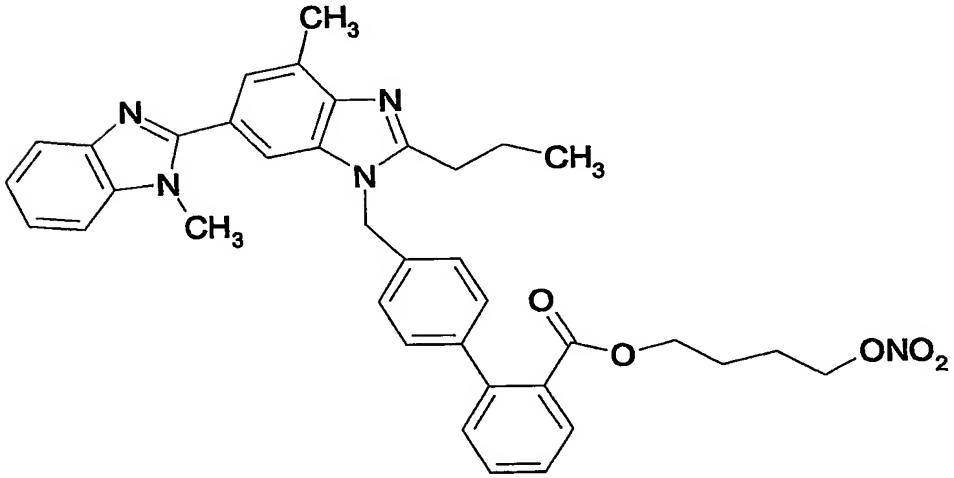

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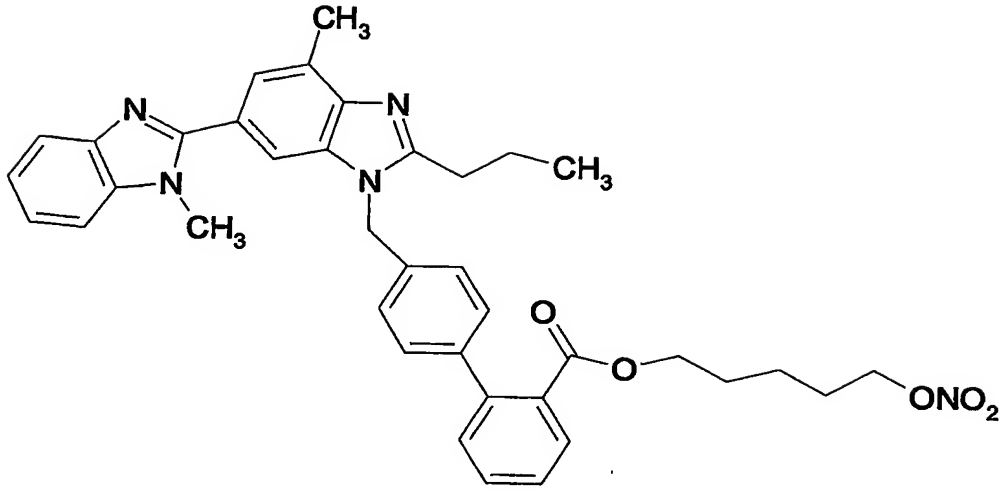

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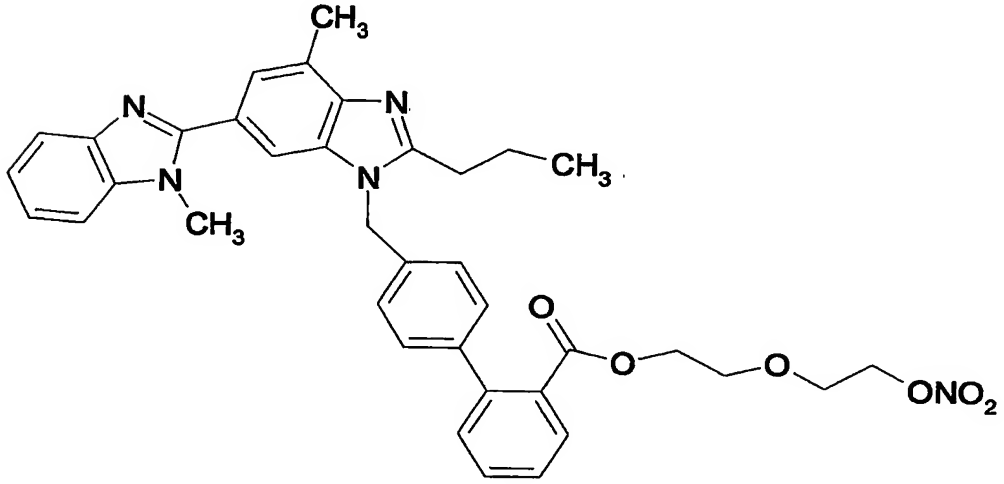

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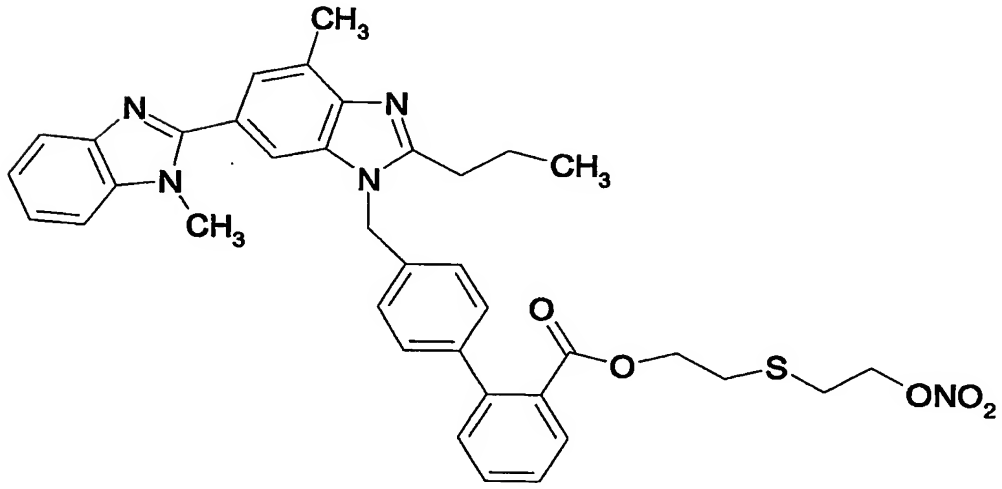

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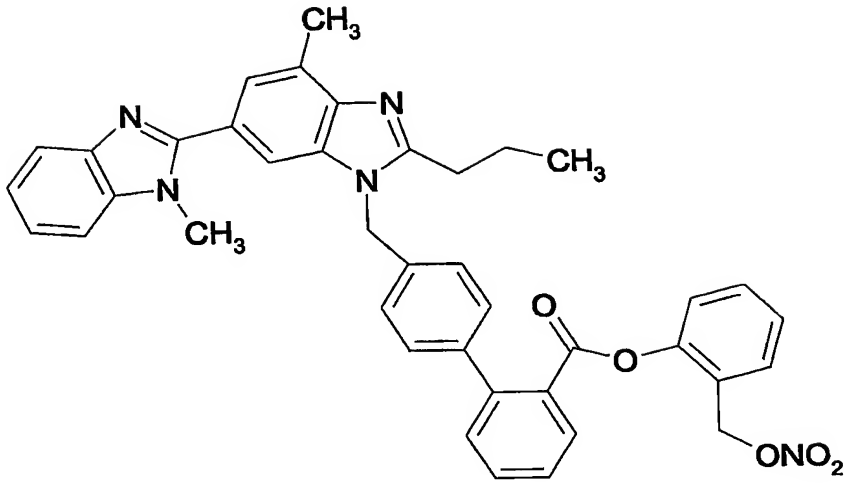

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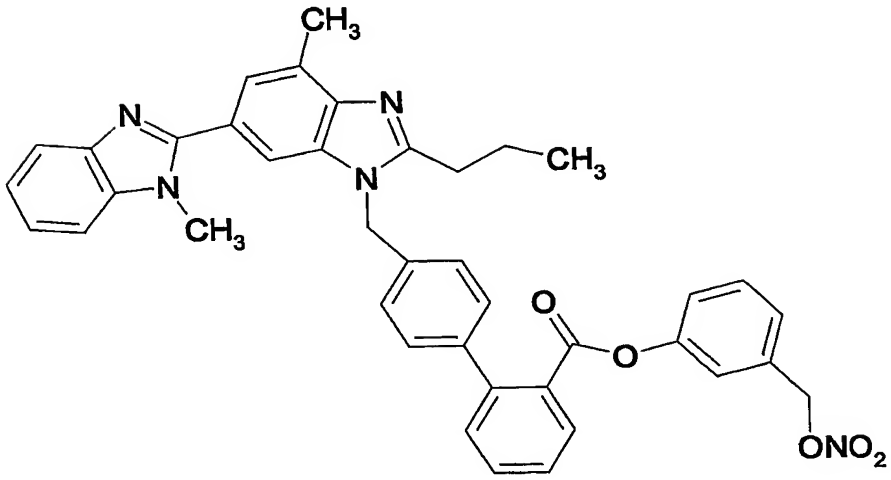

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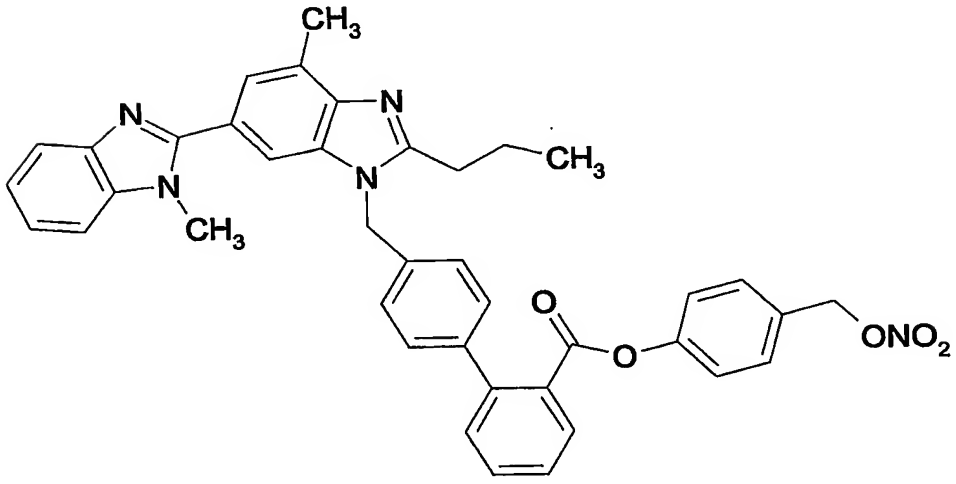

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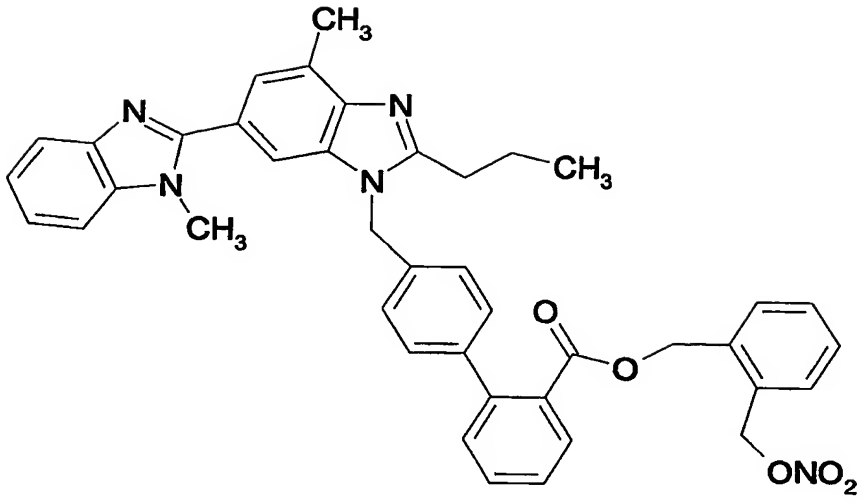

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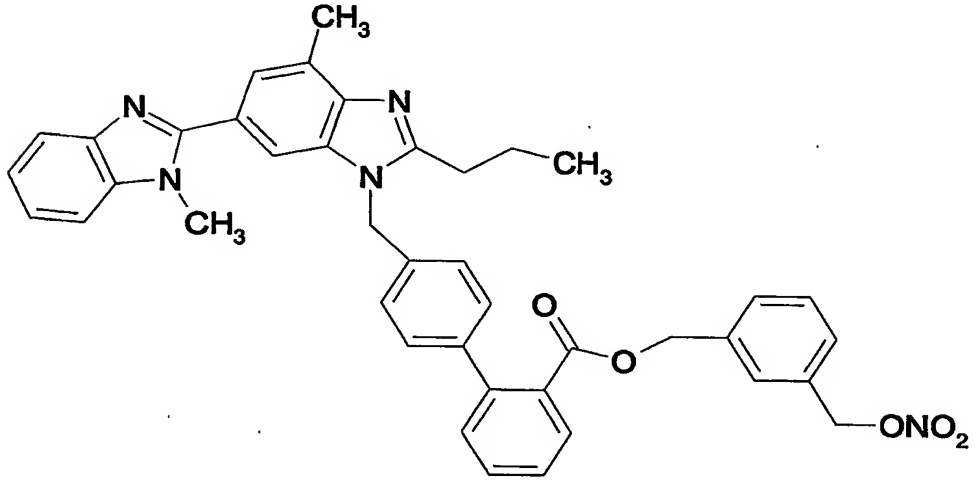

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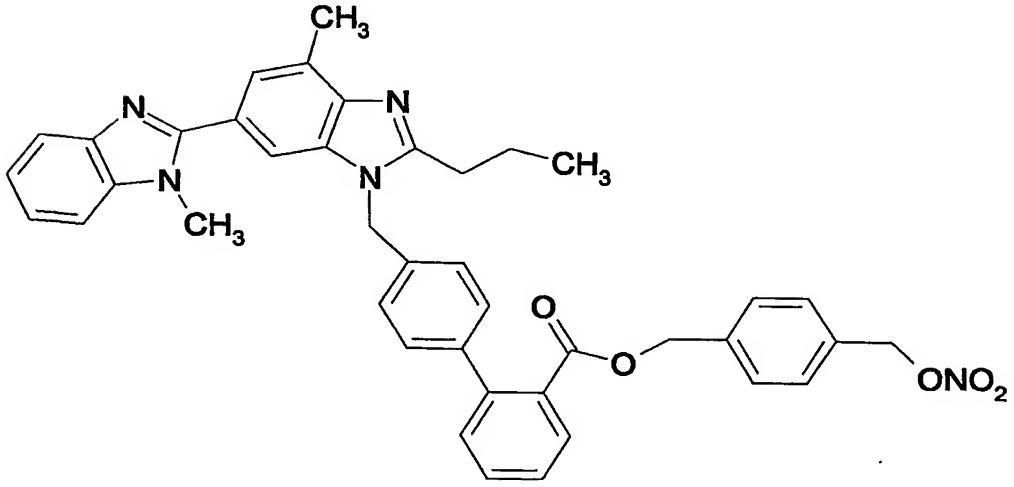

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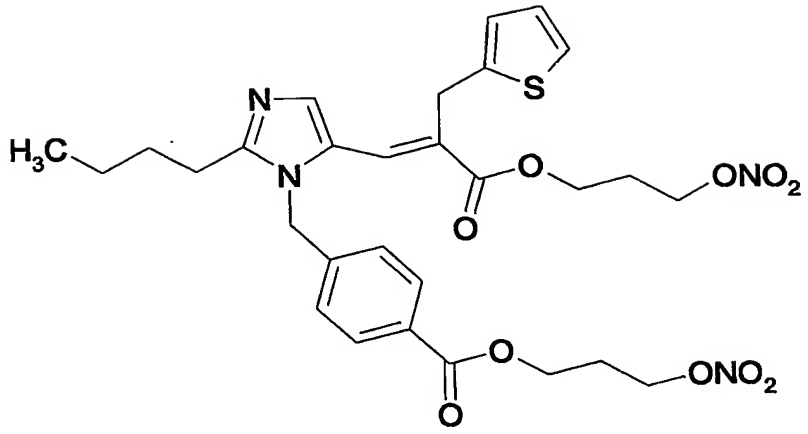

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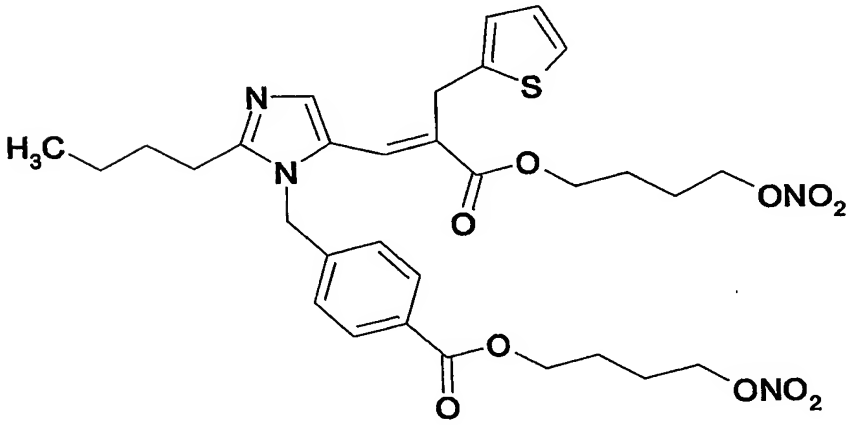

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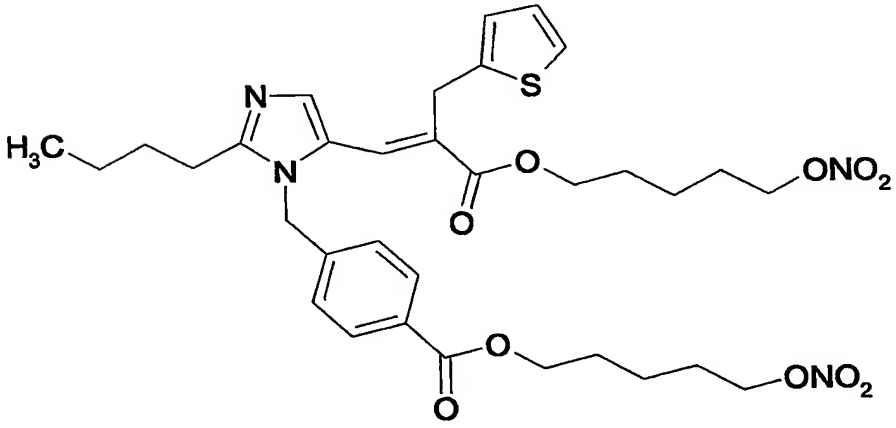

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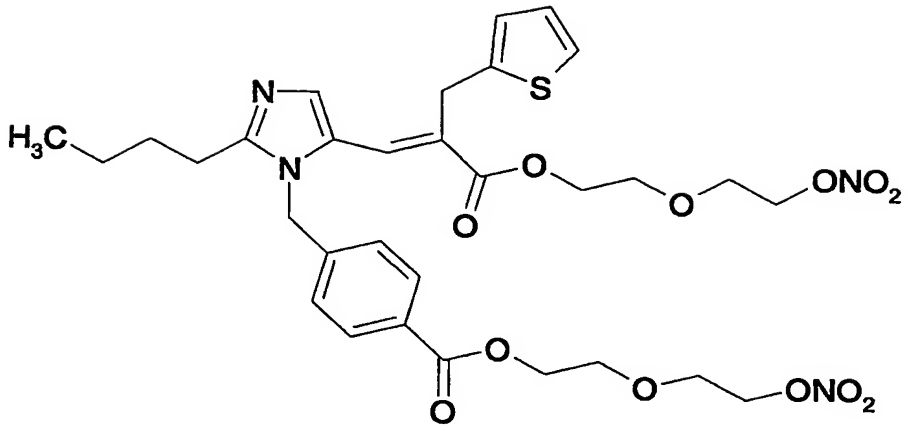

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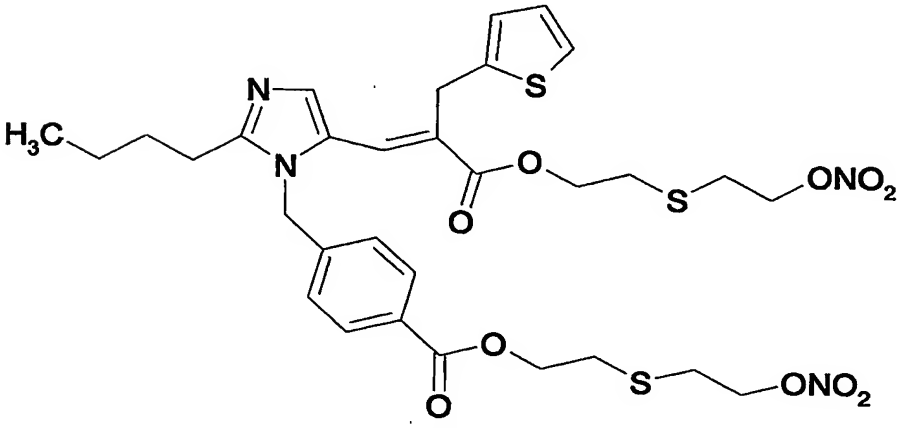

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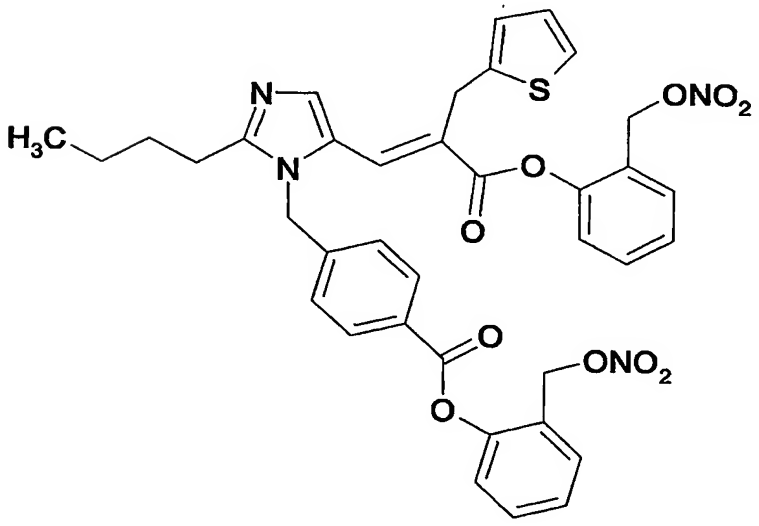

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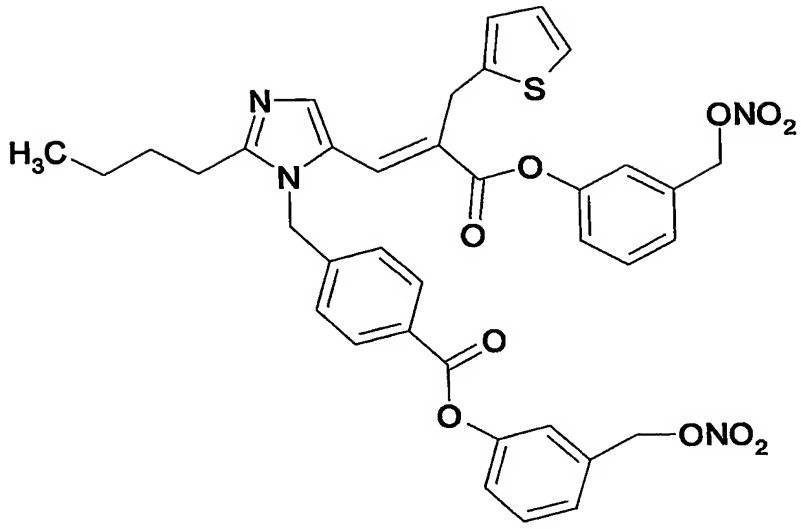

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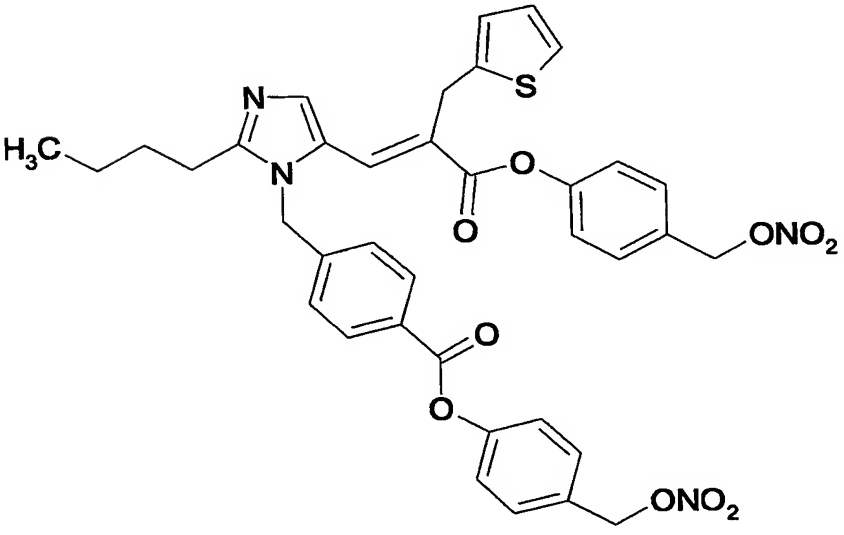

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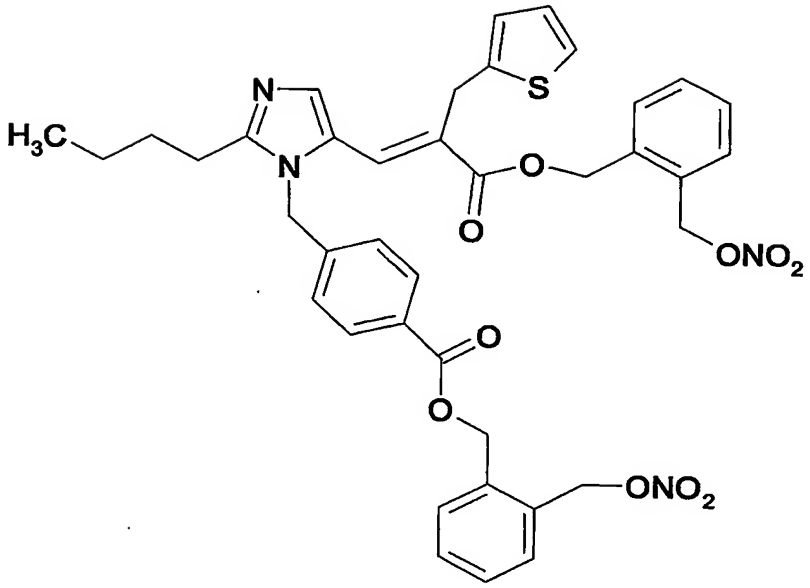

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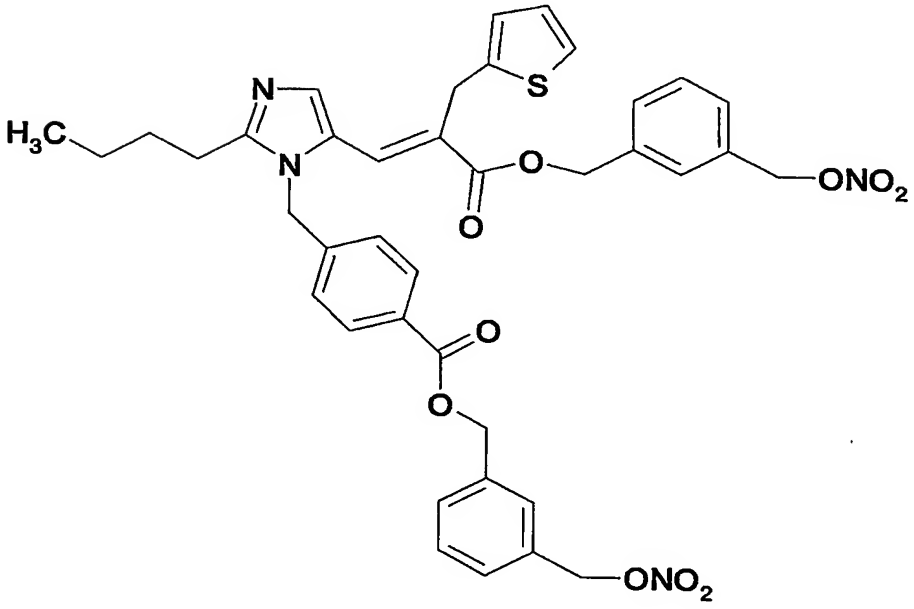

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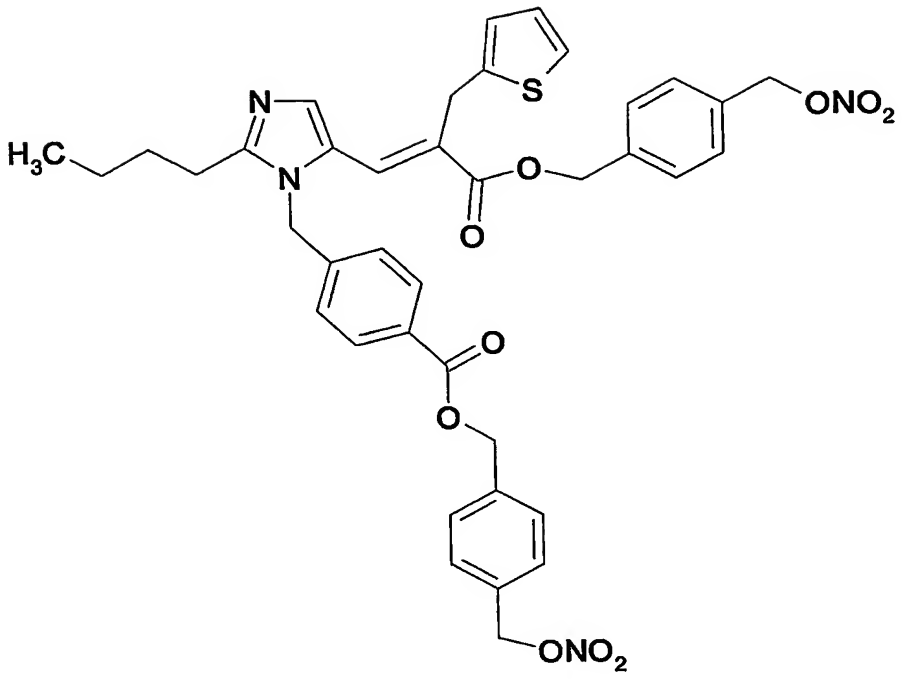

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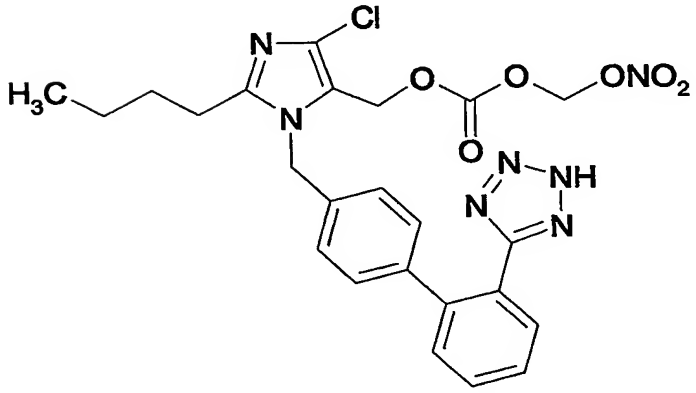

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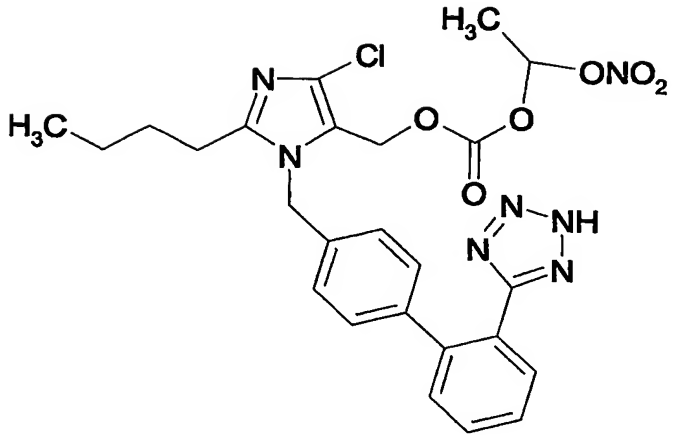

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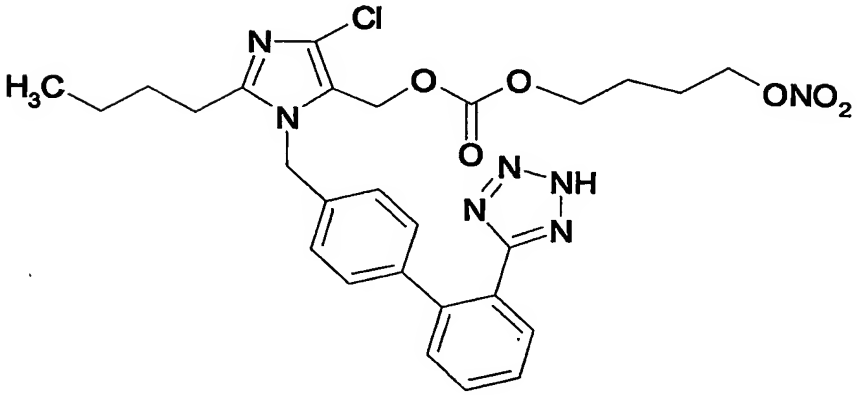

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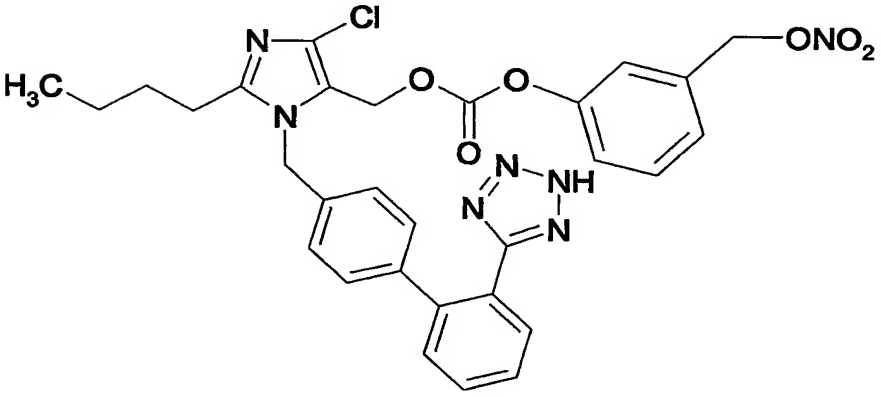

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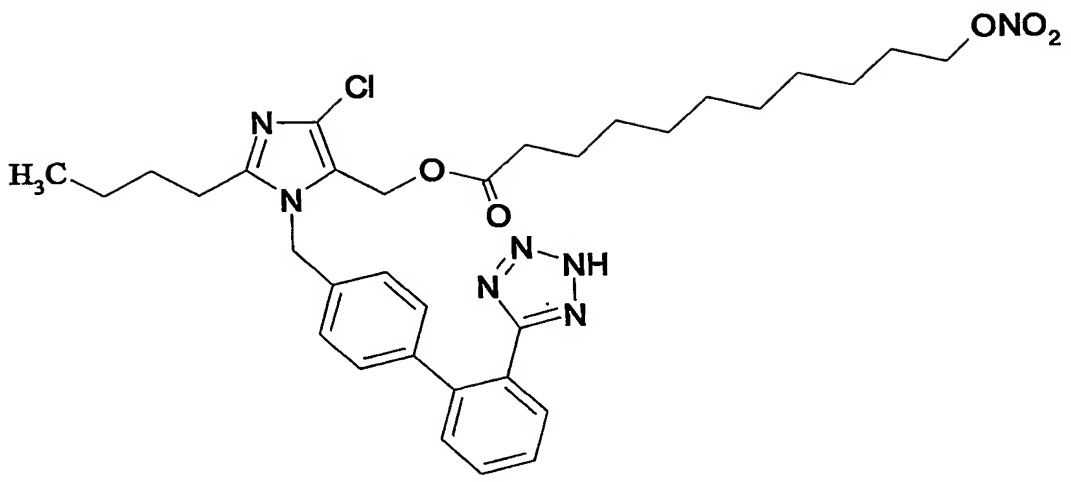


(68)

As mentioned above, object of the present invention are also pharmaceutical compositions containing at least a compound of the present invention of formula (I) together with non toxic adiuvants and/or carriers usually employed in the pharmaceutical field.

The daily dose of active ingredient that should be administered can be a single dose or it can be an effective amount divided into several smaller doses that are to be administered throughout the day. Usually, total daily dose may be in amounts preferably from 50 to 500 mg. The dosage regimen and administration frequency for treating the mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will be selected in accordance with a variety of factors, including for example age, body weight, sex and medical condition of the patient as well as severity of the disease, route of administration, pharmacological considerations and eventual concomitant therapy with other drugs. In some instances, dosage levels below or above the aforesaid range and/or more frequent may be adequate, and

this logically will be within the judgment of the physician and will depend on the disease state.

The compounds of the invention may be administered orally, parenterally, rectally or topically, by inhalation or aerosol, in formulations eventually containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions may be formulated according to known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides, in addition fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the active ingredient with a suitable non-irritating excipient, such as cocoa butter and polyethylene glycols.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or

starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavouring and the like.

The compounds of the present invention can be synthesized as follows.

A) The compound of general formula (I) or a pharmaceutically acceptable salt, as above defined:

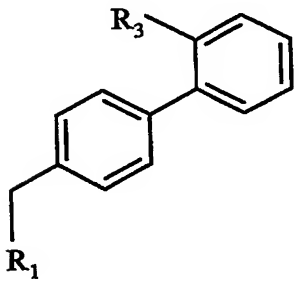
$$R-(Y-ONO_2)_s \qquad (I)$$

when R is the residue of formula (II), can be obtained by a process comprising:

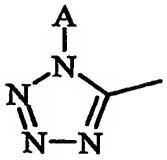
i) reacting a compound of formula (IV):

$$R_2-(Y-Hal)_s \qquad (IV)$$

wherein s = 1 and R_2 is



wherein R_3 is the group of formula (VA):



(VA)

wherein A = H or W, W being a tetrazole protecting group such as trityl, tert-butoxycarbonyl (BOC) and ethyloxycarbonyl or R_3 is -COO-;

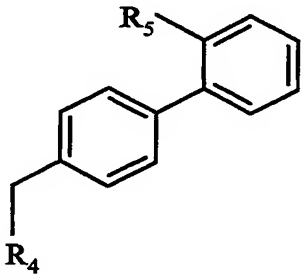
R_1 and Y are as above defined, Hal is an halogen atom preferably Cl, Br or I;

with $AgNO_3$ in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen at temperatures range between 20°-80°C and

ii) optionally acid hydrolysing the tetrazole protecting group W, as well known in the art, for example as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980 and

iii) if desired, converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt thereof.

- The compound of formula (IV) can be obtained by reacting a compound of formula (V):



(V)

wherein R_5 is the group of formula (VA) as above defined or -COOH and R_4 has the same meaning as R_1 with N_0 = -COOH or -OH,

i.1) when R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIa) wherein m = 1 and N_0 = -OH, with a compound of formula (VI) or (VII):

Hal-Y-COHal (VI)

Hal-Y-OCOHal (VII)

wherein Hal and Y are as above defined. The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as THF or CH_2Cl_2 at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C;

The compounds of formula (VI) are commercially available or can be obtained from the corresponding acids by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF, etc. The corresponding acids are commercially available compounds.

The compounds of formula (VII) are commercially available or can be obtained from the corresponding alcohols by reaction with triphosgene in presence of an organic base;

Alternatively, the compound of formula (IV) can be obtained by reacting a compound of formula (V) as defined in i.1), with a compound of formula (VIII) commercially available:

Hal-Y-COOH (VIII)

wherein Hal and Y are as above defined, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C;

i.2) when R_5 is the group (VA) or -COOH, $R_4 = R_1$ and R_1 is selected from the groups (IIa)-(IId) wherein m = 0 and N_0 = -COOH, with a compound of formula (IX):

Hal-Y-OH (IX)

wherein Hal and Y are as above defined, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or

N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C; The compounds of formula (IX) are commercially available.

Alternatively, transforming the group -COOH into an activated acyl chloride or into another group suitable for esterification, according to methods well known in the literature, and carrying out the esterification in presence of a organic or inorganic base in an aprotic polar/non-polar solvent such as THF or CH_2Cl_2 at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C;

A1) Alternatively, the compounds of formula (I) as above defined, when R is the residue of formula (II), can be obtained by reacting compounds of formula (V) as above defined:

i.1.1) when R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIa) wherein m = 1 and N_0 = -OH, with a compound of formula (X):

$$O_2NO-Y-COOH \quad (X)$$

in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C.

The compounds of formula (X) can be obtained from the corresponding alcohols by reaction with nitric acid and acetic anhydride in a temperature range from -50°C to 0°C or reacting the corresponding halogen derivatives of formula (VIII) with $AgNO_3$ as already described.

i.2.1) when R_5 is the group (VA) or -COOH, $R_4 = R_1$ and R_1 is selected from the groups (IIa)-(IId) wherein m = 0 and N_0 = -COOH, with a compound of formula (XI):

$$O_2NO-Y-OH \quad (XI)$$

wherein Y is as above defined; in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C. The compound of formula (XI) can be obtained by reacting a compound of formula (IX) with $AgNO_3$ in a suitable organic solvent such as acetonitrile or THF under nitrogen at temperatures range between 20°-80°C.

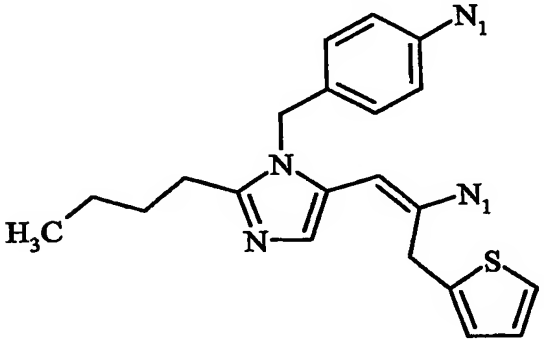
B) The compound of general formula (I), when R is the residue of formula (III), can be obtained by reacting a compound of formula (XII):

$$R_6-(Y-Hal)_s \qquad (XII)$$

wherein s = 2, R_6 is the residue (III) and N_1 is -COO-, Y and Hal are as above defined,

with $AgNO_3$ as already described.

Compounds of formula (XII) are obtained by reacting a compound of formula (XIII):



(XIII)

wherein N_1 is -COOH with compounds of formula (IX) as above defined:

$$Hal-Y-OH \qquad (IX)$$

in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C as already described.

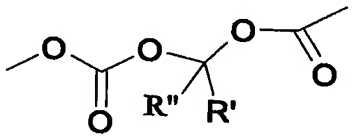
Alternatively, transforming the group -COOH (N_1) into an activated acyl chloride or into another group suitable for esterification, according to methods well known in the literature, and carrying out the esterification in presence of a organic or inorganic base in an aprotic polar/non-polar solvent such as THF or CH_2Cl_2 at a temperature in the range between 0°-65°C or in a double phase system.

B1) Alternatively, the compounds of general formula (I) as above defined, when R is the residue of formula (III), can be obtained by reacting the compound of formula (XIII) with a compound of formula (XI) as above defined:

$$O_2NO\text{-}Y\text{-}OH \quad (XI)$$

in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C.

C) The compounds of formula (I), as above defined, when s =1 and R is the residue of formula (II), wherein R_0 is the tetrazole goup and R_1 is the group (IIa) wherein m = 1 and N_0 is



wherein R' and R'' are as above defined,

can be obtained by reacting a compound of formula (IVa):

$$R_2\text{-}(CR'R''\text{-}Hal)_s \quad (IVa)$$

wherein s =1, R_2 and Hal are as above defined, R_3 is the group (VA), R_1 is the group (IIa) wherein m = 1 and N_0 is -OCOO-,

with a compound of formula (X) as above defined, in presence of an organic or inorganic base in a polar solvent

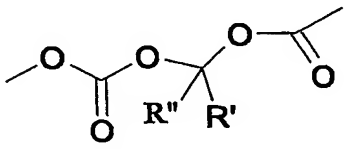
as DMF, THF, acetonitrile at a temperature in the range from -5°C to 60°C or in a double phase system as already known in the literature.

The compounds (IVa) can be obtained by reacting a compound of formula (V) as above defined, wherein R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIa) wherein m = 1 and N_0 = -OH, with a compound of formula (VIIa):

$$Hal\text{-}CR'R''\text{-}OCOHal \quad (VIIa)$$

as already described for the compounds (IV); and optionally acid hydrolysing the tetrazole protecting group as above described.

D) The compounds of formula (I), as above defined, when s =1 and R is the residue of formula (II), wherein R_0 is the tetrazole goup and R_1 is the group (IIc) wherein N_0 is



wherein R′ and R′′ are as above defined,

can be obtained by reacting a compound of formula (V), wherein R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIc) wherein N_0 = -COOH, with a compound of formula (XIV):

$$Hal\text{-}CR'R''\text{-}OCOO\text{-}Y\text{-}ONO_2 \quad (XIV)$$

wherein Hal, Y, R′ and R′′ are as above defined,

in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from -5°C to 60°C or in a double phase system as already known in the literature.

Compounds of formula (XIV) can be obtained by reacting compounds (XI) with compounds (VIIa) as above defined.

The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as THF or CH_2Cl_2

at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C; and optionally acid hydrolysing the tetrazole protecting group as above described.

The following examples are to further illustrate the invention without limiting it.

Example 1

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxymethylbenzoic acid ester (corresponding to compound (4))

A solution of triphenylmethyl chloride (1.31 g, 4.70 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of Losartan potassium salt (2.0 g; 4.34 mmol) in CH_2Cl_2 (38 ml) and THF (12 ml). The resulting mixture was stirred at room temperature for 24 hours. Then brine (15 ml) was added and the product was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Et_2O 30:1) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol** (1.73 g, 60%).

From this compound the title compound **(4)** can be achieved through two different synthetic procedure:

Synthetic procedure A

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-nitrooxymethylbenzoic acid (0.66 g, 3.38 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH_2Cl_2 (20 ml)

and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH_2Cl_2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (CH_2Cl_2/Et_2O 10:1) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxymethylbenzoic acid ester** (1.2 g, 55%).

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxymethylbenzoic acid ester (1.2 g, 1.42 mmol) in CH_2Cl_2 (8 ml) a saturated solution of HCl in Et_2O (20 ml) was added. The reaction was stirred at room temperature for 5 hours then the title compound **(4)** was filtered off and purified by crystallization with CH_2Cl_2 (0.304 g, 36 %).

^{1}H-NMR (DMSO-d_6): 7.73-7.56 (7H,m); 7.24 (1H,d); 7.00(4H,m); 5.60(2H,s); 5.39(2H,s); 5.28(2H,s); 2.61(2H,t); 1.53(2H,m); 1.28(2H,m); 0.82(3H,t).

Synthetic procedure B

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-bromomethylbenzoic acid (0.722 g, 3.35 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH_2Cl_2 (20 ml) and THF (6 ml) a solution of dicyclohexylcarbodiimide (0.644 g, 3.12 mmol) in CH_2Cl_2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the

organic phase was concentrated. The crude material was purified by silica gel chromatography (CH_2Cl_2/Et_2O 10:1) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromomethylbenzoic acid ester** (1.56 g, yield 70%).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromomethylbenzoic acid ester (0.807 g, 0.936 mmol) was dissolved in CH_3CN (15 ml) and silver nitrate (0.305 g, 1.8 mmol) was added, in the dark and under nitrogen. The mixture was stirred at 40° C for 6 hours. Then the precipitated silver salts were filtered off and the organic phase was diluted with CH_2Cl_2 and washed with H_2O, brine, dried over Na_2SO_4 and concentrated, affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitromethylbenzoic acid ester** (0.553 g, 70%).

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitromethylbenzoic acid ester by acid hydrolysis as above described, the title compound **(4)**, after crystallization in CH_2Cl_2, was obtained (0.304 g, 77%).

Example 2

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (corresponding to compound (2))

This compound can be achieved through two different synthetic procedure:

Synthetic procedure A

To a solution of 2-butyl-4-chloro-1-[[2′-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-nitrooxybutanoic acid (0.536 g, 3.6 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH_2Cl_2 (20 ml) and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH_2Cl_2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (CH_2Cl_2/Et_2O 10:1) affording **2-butyl-4-chloro-1-[[2′-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (1.45 g, 70%).

To a solution of 2-butyl-4-chloro-1-[[2′-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (1.0 g, 1.25 mmol) in CH_2Cl_2 (10 ml) a saturated solution of HCl/Et_2O (22 ml) was added. The reaction was stirred at room temperature for 5 hours then the title compound **(2)** was filtered off and purified by crystallization in Et_2O/n-hexane (0.507 g, yield 71%).

^{1}H-NMR (DMSO-d_6): 7.66 (2H,d); 7.57 (1H,d); 7.49 (1H,d); 7.09 (2H,d); 6.95 (2H,d); 5.25 (2H,s); 4.99 (2H,s); 4.49 (2H,t); 2.54 (2H,t); 2.01 (2H,t); 1.60 (2H,m); 1.49 (2H,m); 1.32 (4H,m); 0.84 (3H,t).

Synthetic procedure B

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-bromobutanoic acid (0.561 g, 3.36 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH_2Cl_2 (20 ml) and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH_2Cl_2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (CH_2Cl_2/Et_2O 10:1) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester** (1.27 g, yield 60%).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester (1.2 g, 1.47 mmol) was dissolved in CH_3CN (20 ml) and silver nitrate (0.475 g, 2.8 mmol) was added in the dark and under nitrogen. The mixture was stirred at 60° C for 8 hours. The precipitated silver salts were filtered off and the organic phase was diluted with CH_2Cl_2 and washed with H_2O, brine, dried over Na_2SO_4 and concentrated, affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (0.819 g, yield 70%).

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester by acid hydrolysis as above

described, the title compound **(2)**, after crystallization with Et_2O/n-hexane was obtained (0.507 g, 71 %).

Example 3

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester (corresponding to compound (68))

Using procedure **A** but starting from 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol) and 11-nitrooxyundecanoic acid (0.78 g, 3.36 mmol), **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester** (1.65 g, 80%) was obtained. From acid hydrolysis of this compound (1.6 g, 2.0 mmol) **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester** (0.91 g,70%) was obtained after crystallization from Et_2O/n-Hexane.

(DMSO): 7.66(2H,d); 7.57(1H,d); 7.59(1H,d); 7.09(2H,d); 6.95(2H,d); 5.25(2H,s); 4.99(2H,s); 4.49(2H,t);2.54(2H,t); 2.01(2H,t); 1.62(2H,m); 1.49(2H,m); 1.35-1.14(16H,m); 0.84(3H,t).

CLAIMS

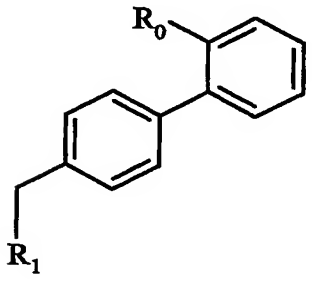
1. A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof:

$$R-(Y-ONO_2)_s \quad (I)$$

wherein:

s is an integer equal to 1 or 2;

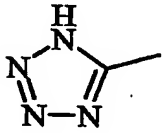
R is selected from the following Angiotensin II Receptor Blocker residues of formula (II) or (III):



(II)

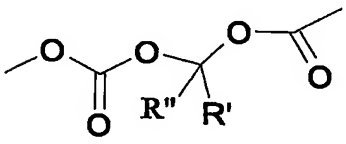
wherein:

R_0 is



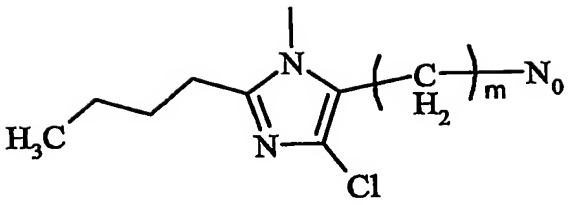
or $-N_0$ which is a group capable to bind to Y, having one of the following meaning:

-COO-, -O-, -CONH-, -OCO-, -OCOO- or

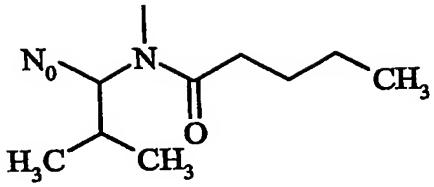


wherein R′ and R′′ are the same or different, and are H or straight or branched C_1-C_4 alkyl;

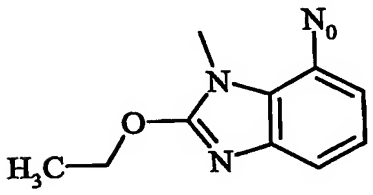
R_1 is selected from the group consisting of:



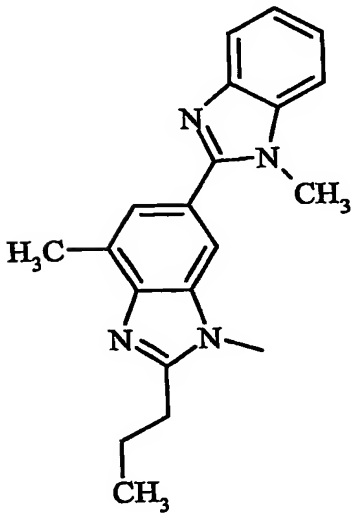
(IIa)



(IIb)

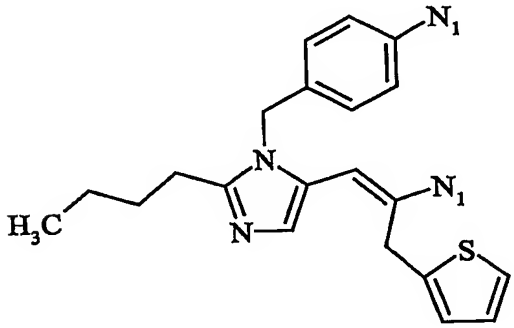


(IIc) or



(IId)

wherein m is an integer equal to 0 or 1 and N_0 is as above defined;



(III)

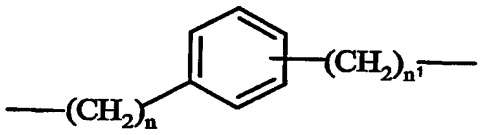
wherein N_1 has the same meaning as N_0 or is equal to -COOH; with the proviso that at least one of the groups N_1 is equal to -COO- or -CONH-, i.e. it is a group capable to bind to Y;

Y is a bivalent radical having the following meaning:

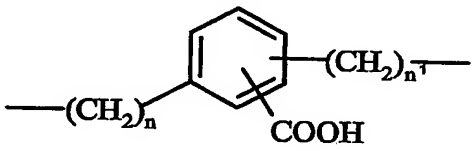
a)

- straight or branched C_1-C_{20} alkylene;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably CH_3;

b)

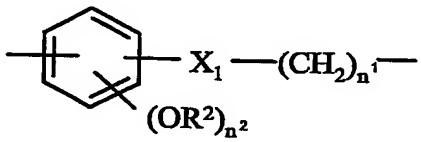


c)



wherein n is an integer from 0 to 20, and n^1 is an integer from 1 to 20;

d)

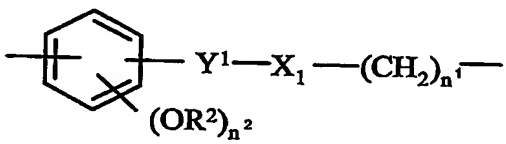


wherein:

n^1 is as defined above and n^2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

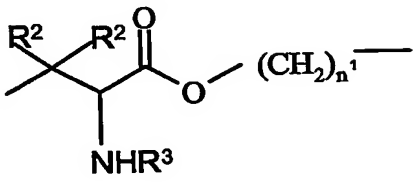


wherein:

n^1, n^2, R^2 and X_1 are as defined above;

Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n^2}-$;

f)



wherein:

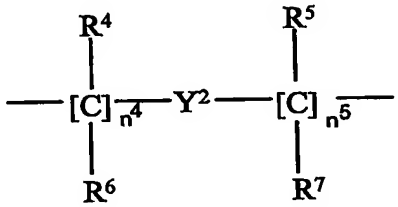
n^1 and R^2 are as defined above, R^3 is H or $-COCH_3$;

with the proviso that when Y is selected from the bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-CH_2$ group;

g)

wherein X_2 is $-O-$ or $-S-$, n^3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as defined above;

h)



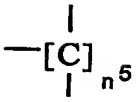
wherein:

n^4 is an integer from 0 to 10;

n^5 is an integer from 1 to 10;

R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^4, R^5, R^6, R^7 are H;

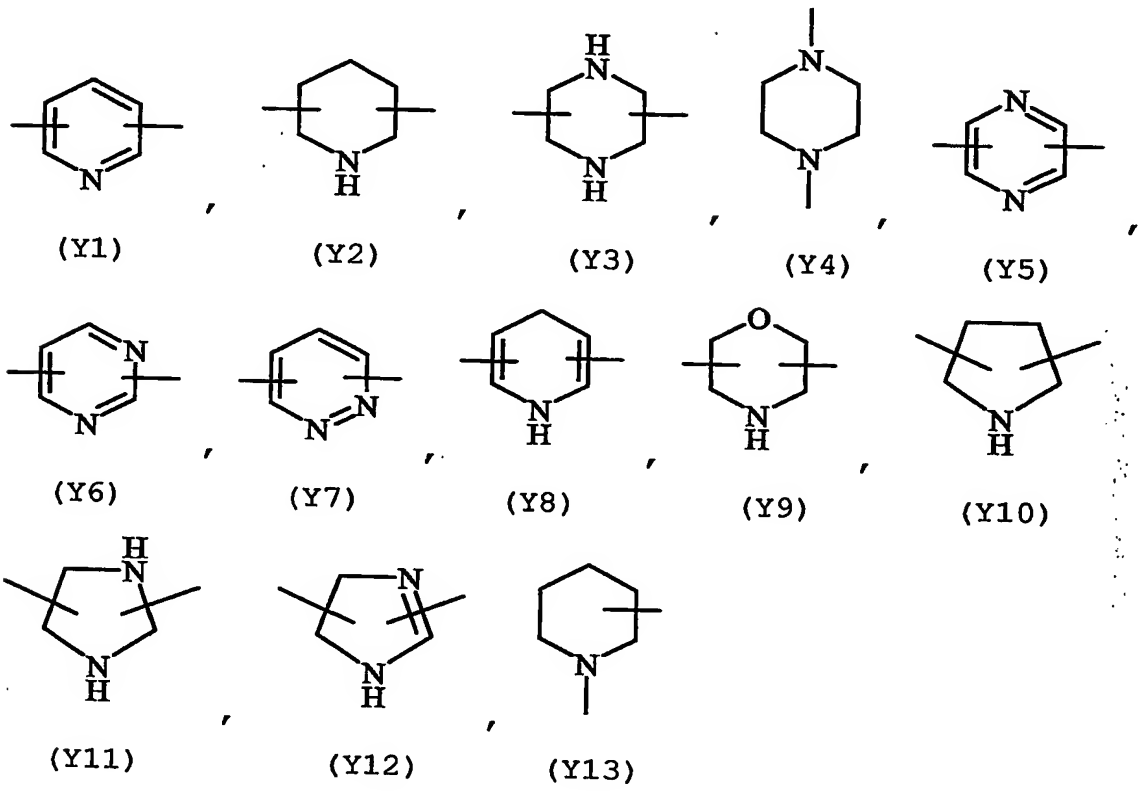
wherein the $-ONO_2$ group is linked to



wherein n^5 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

and is selected from



(Y1), (Y2), (Y3), (Y4), (Y5)

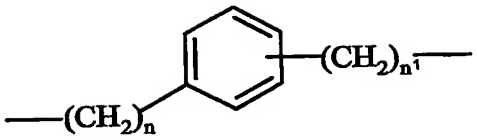
(Y6), (Y7), (Y8), (Y9), (Y10)

(Y11), (Y12), (Y13)

2. A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof according to claim 1 wherein Y is a bivalent radical having the following meaning:

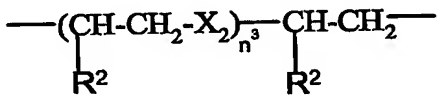
a) straight or branched C_1-C_{10} alkylene;

b)



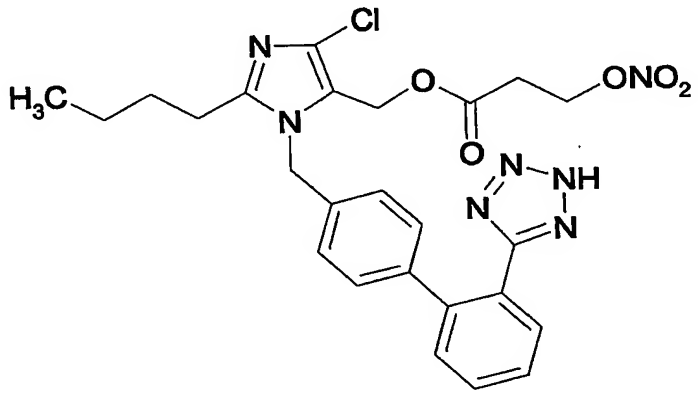
wherein n is an integer equal to 0 or 1, and n^1 is an integer equal to 1; with the proviso the $-ONO_2$ group is linked to a $-CH_2$ group;

g)

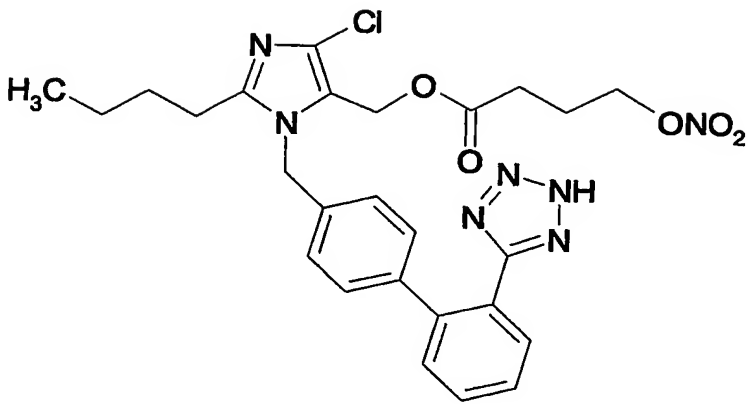


wherein X_2 is -O- or -S-, n^3 is an integer equal to 1 and R^2 is H.

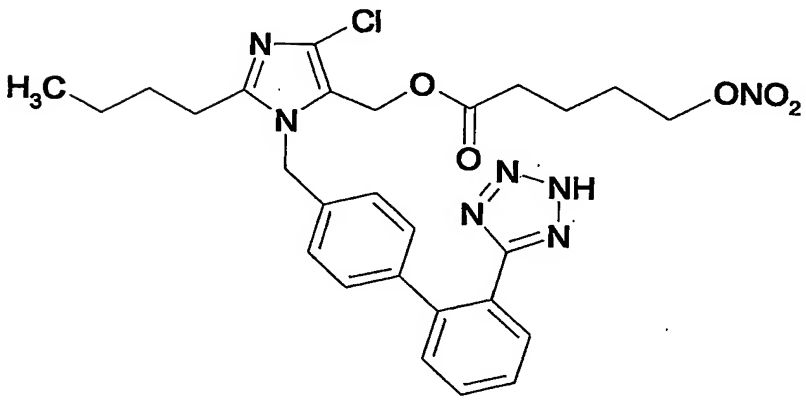
3. A compound according to claims 1-2, selected from the group consisting of:



(1)



(2)



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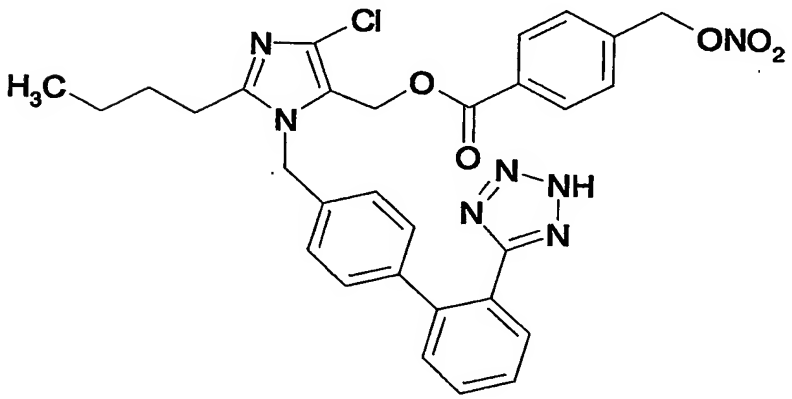

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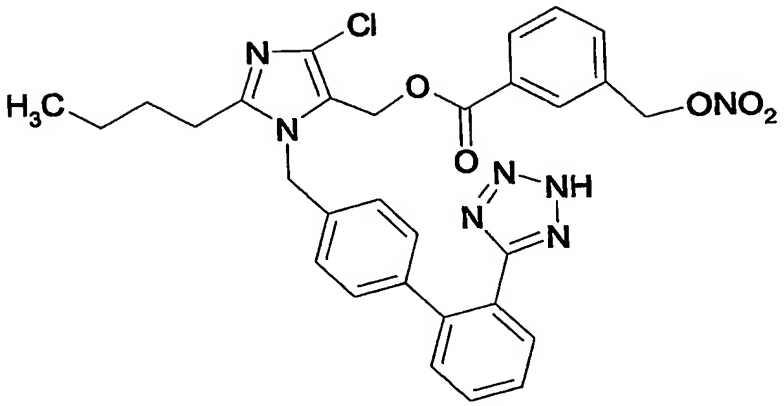

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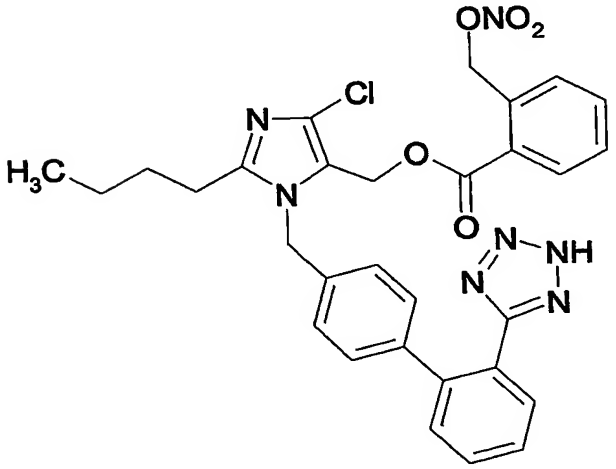

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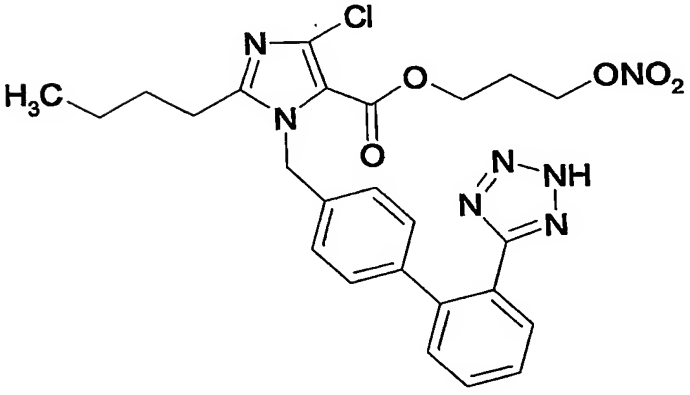

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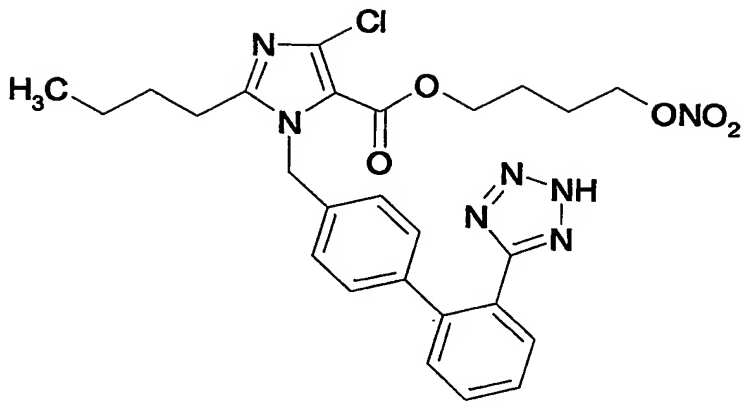

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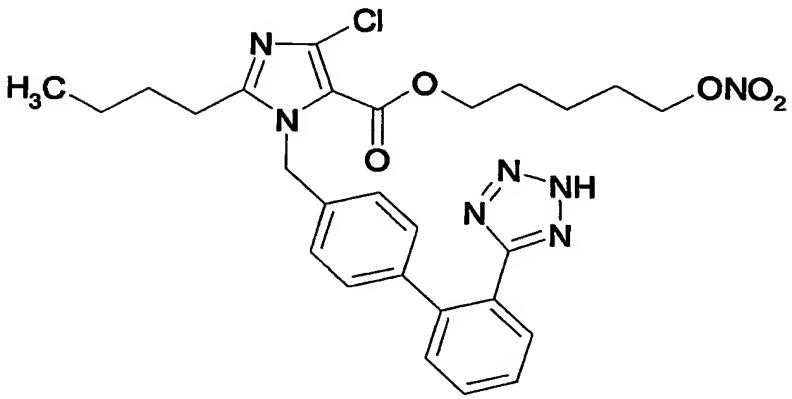

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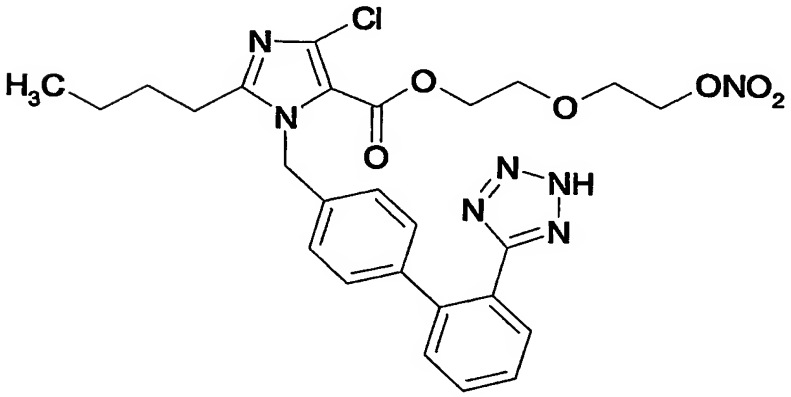

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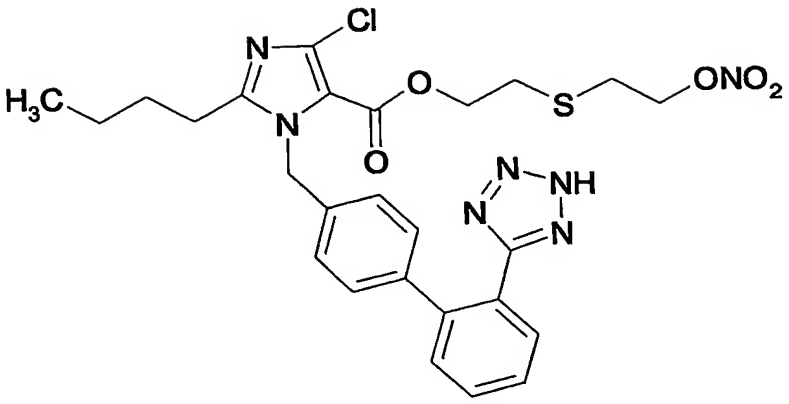

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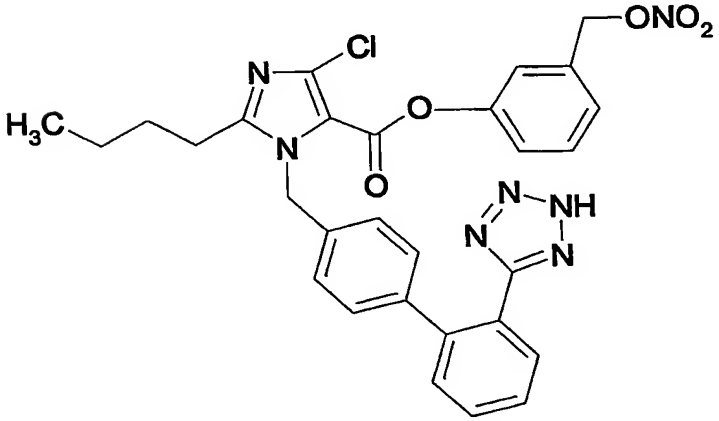

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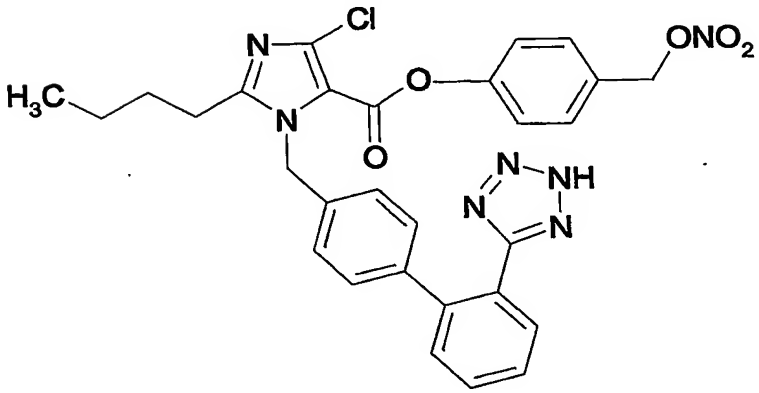

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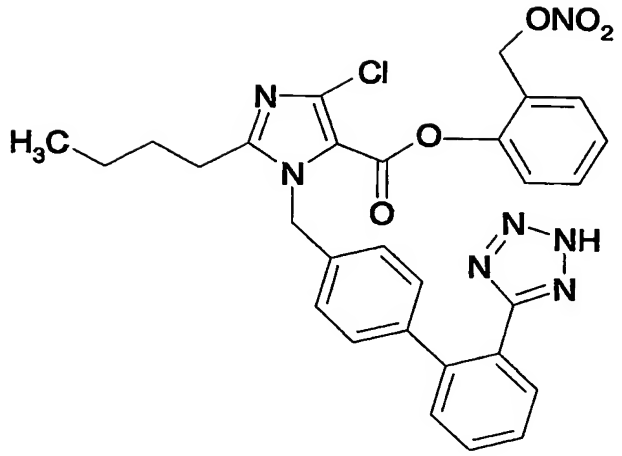

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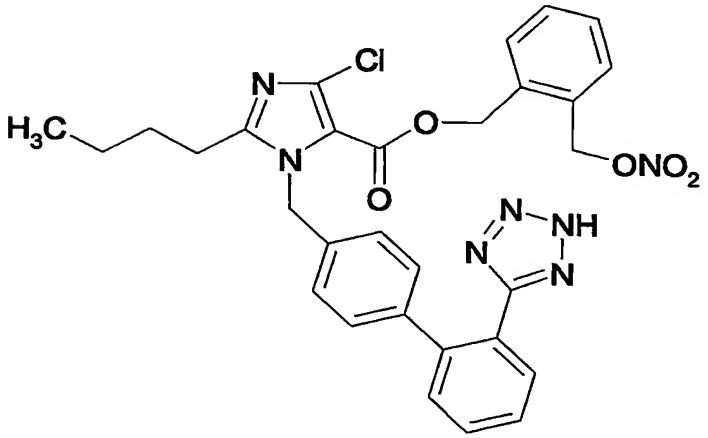

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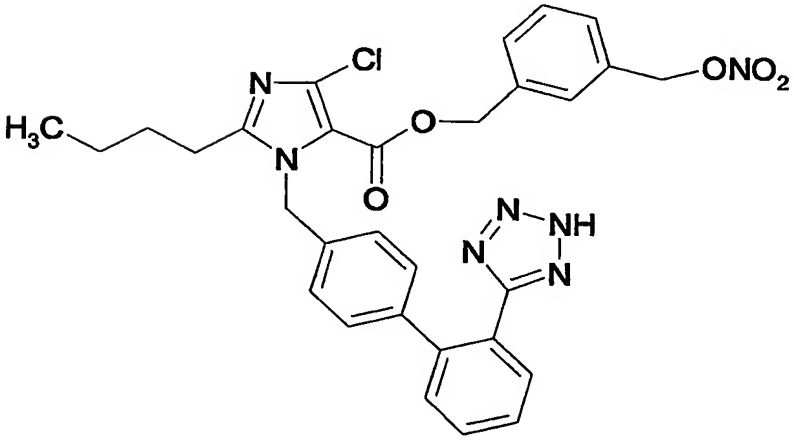

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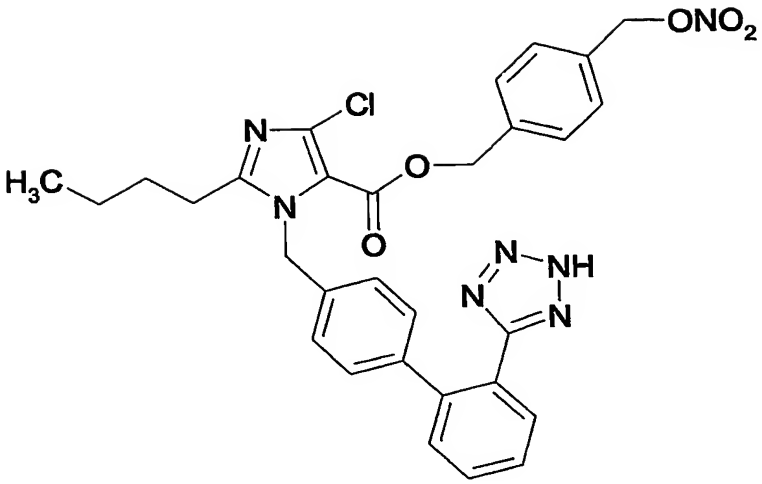

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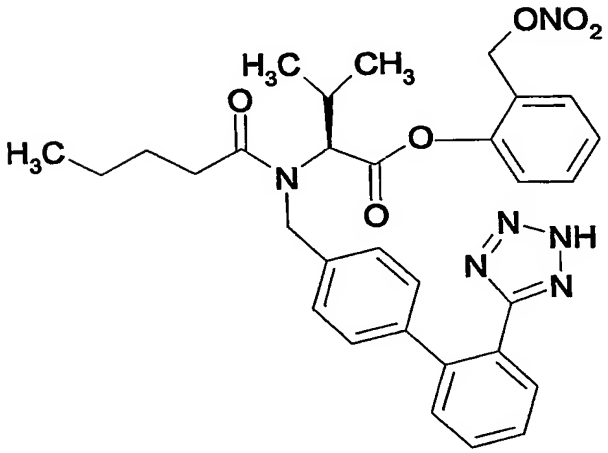

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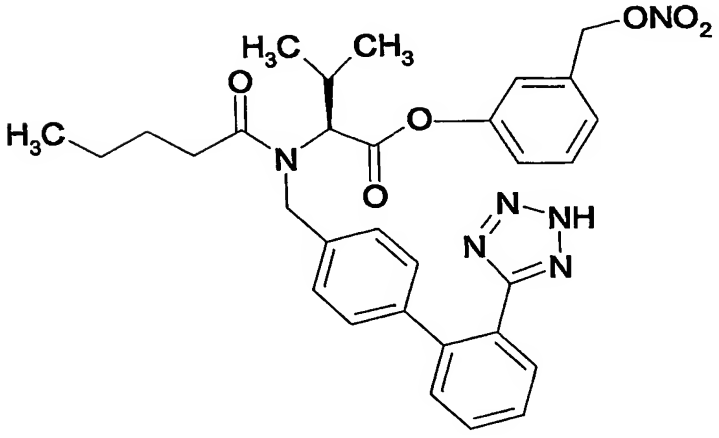

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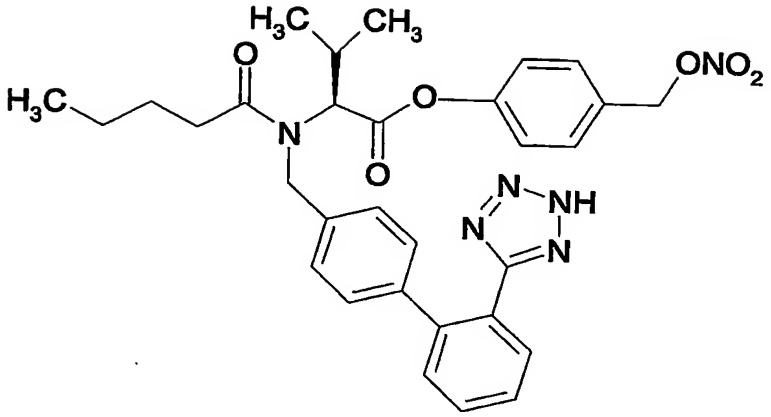

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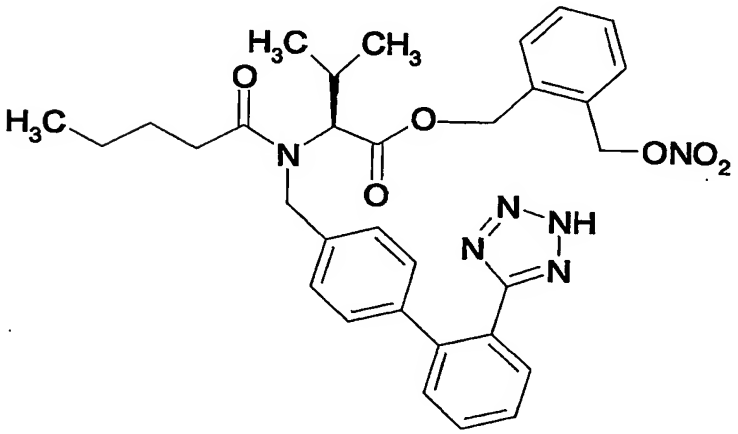

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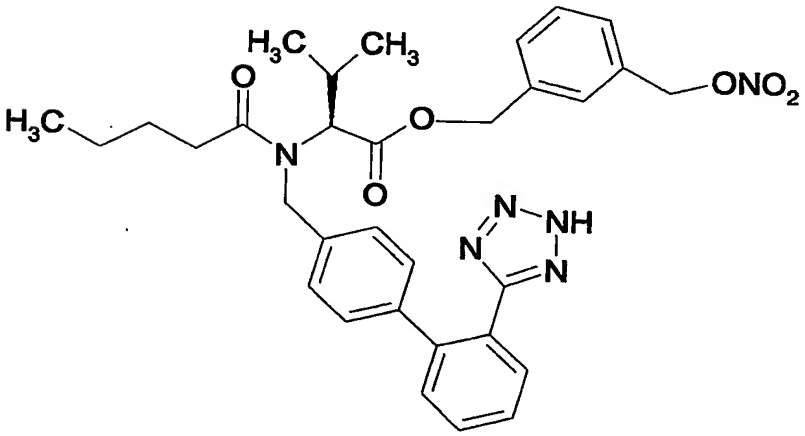

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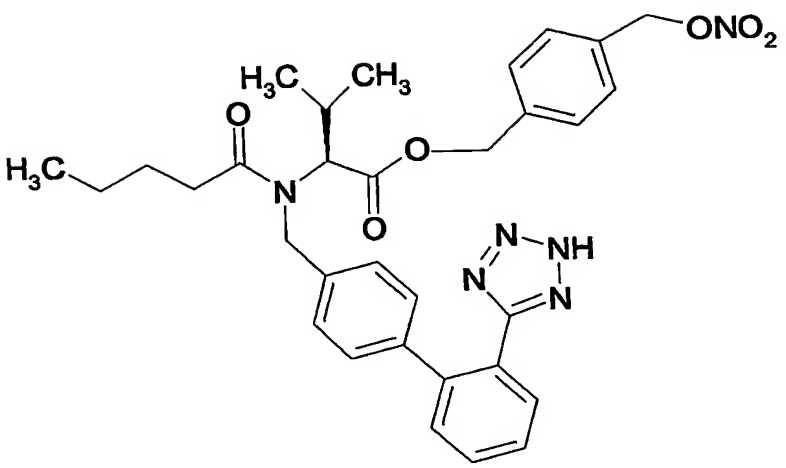

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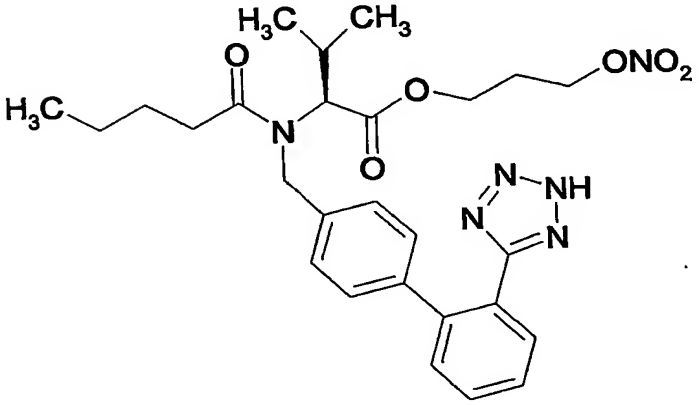

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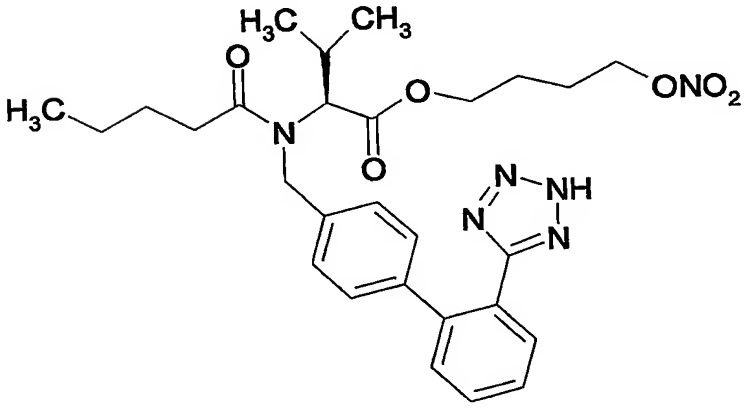

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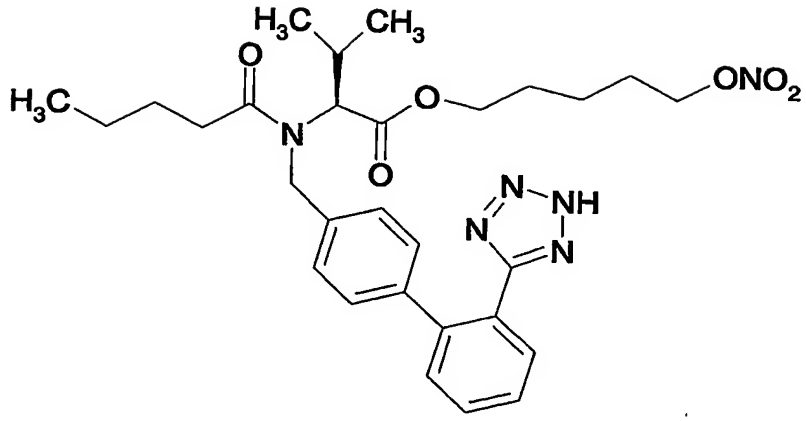

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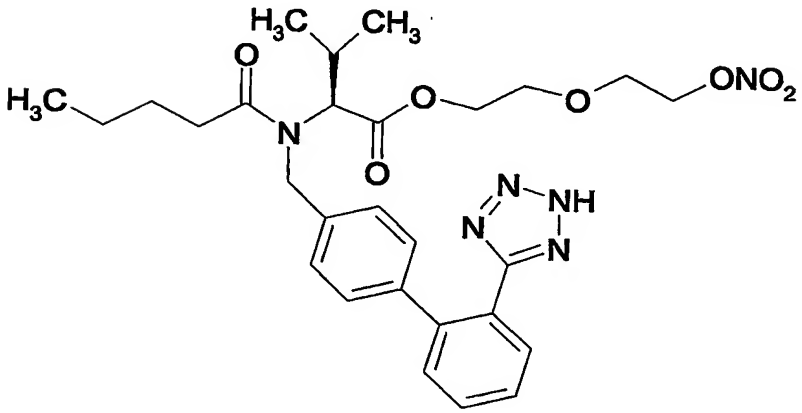

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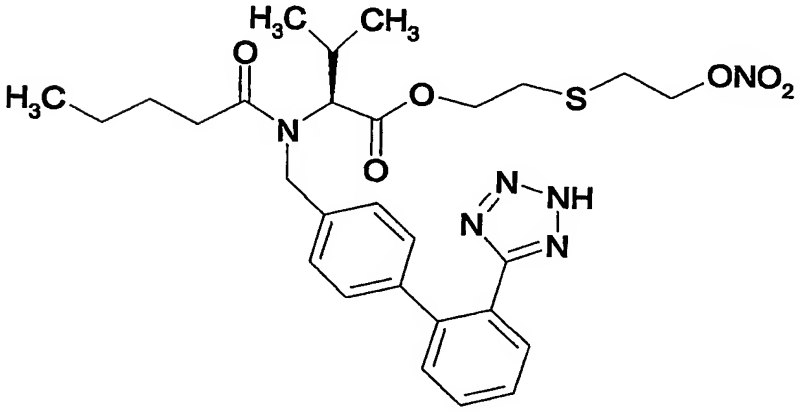

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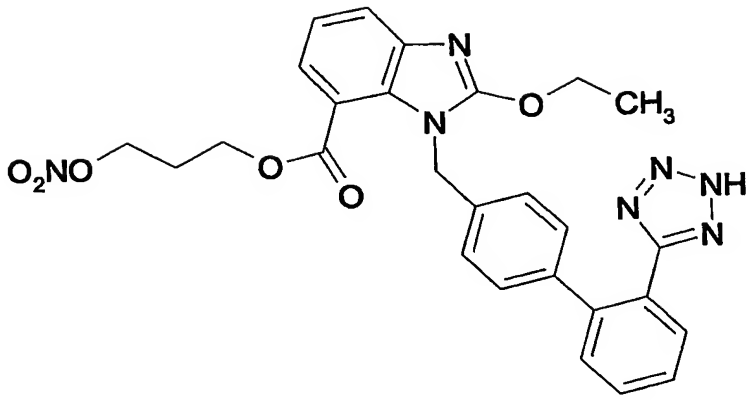

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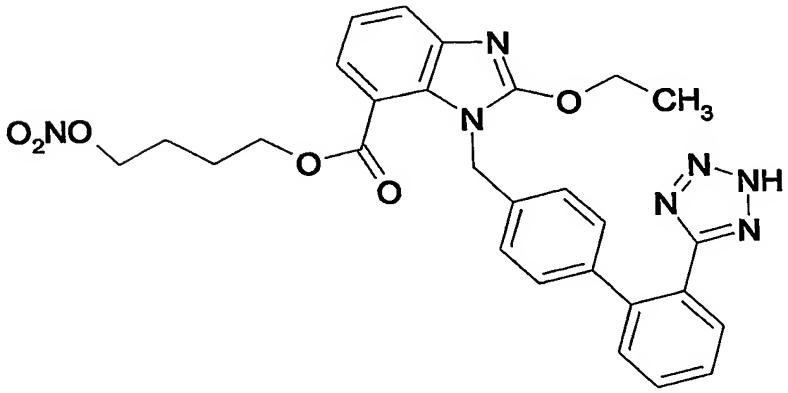

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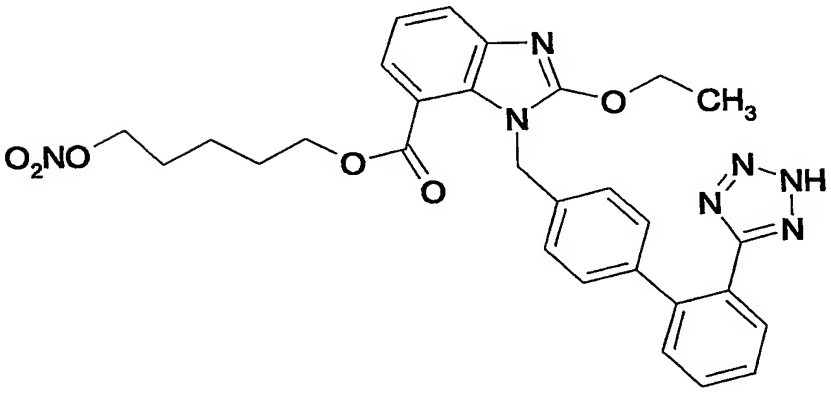

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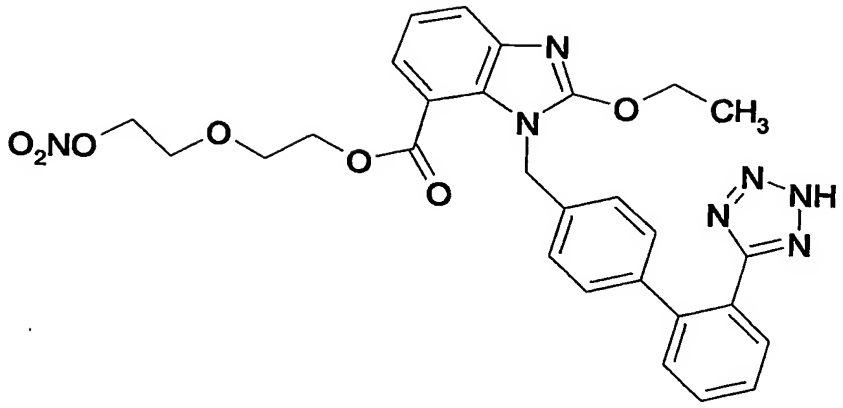

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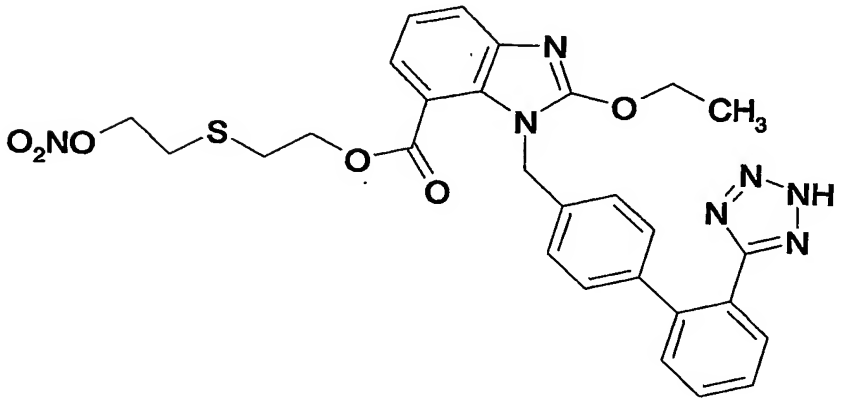

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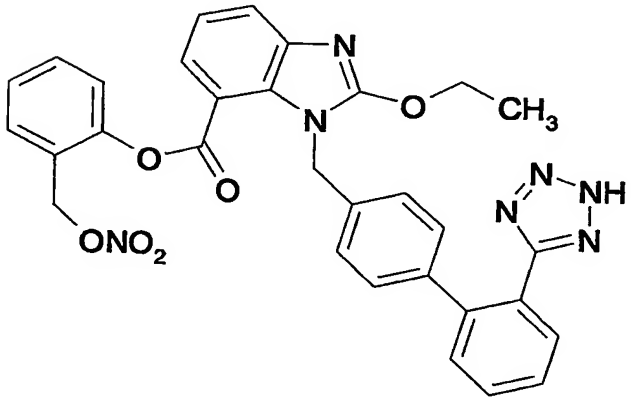

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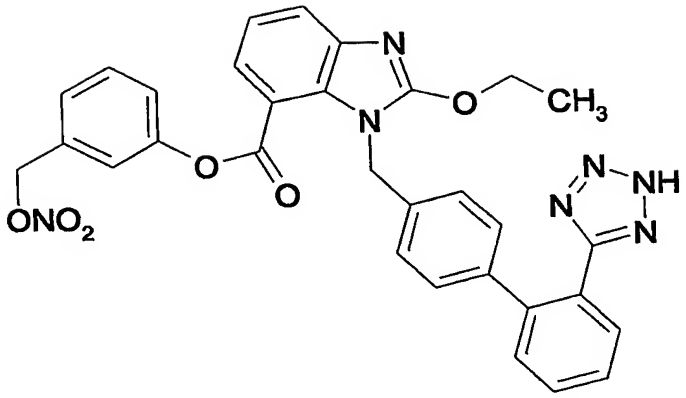

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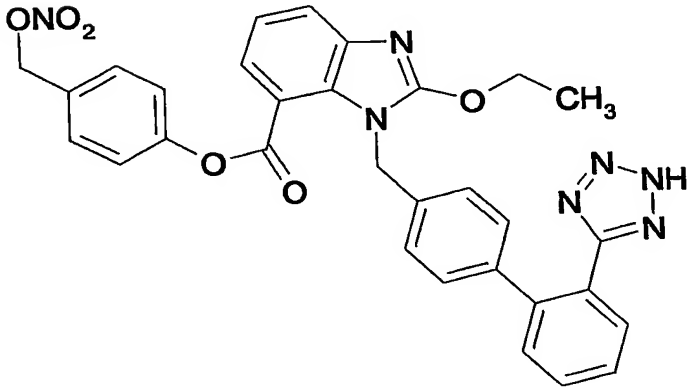

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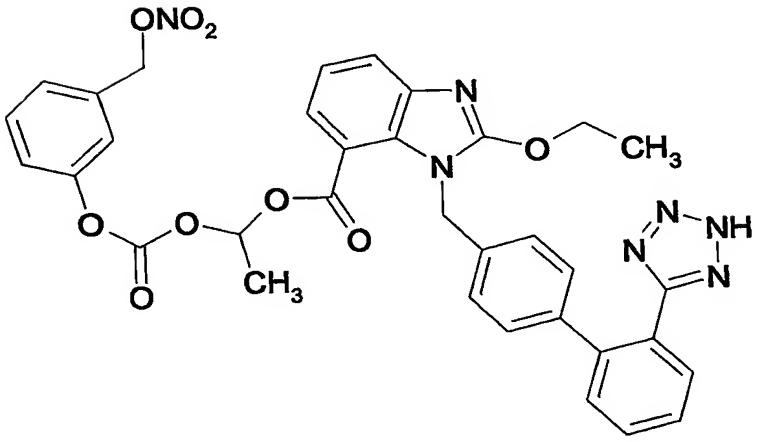

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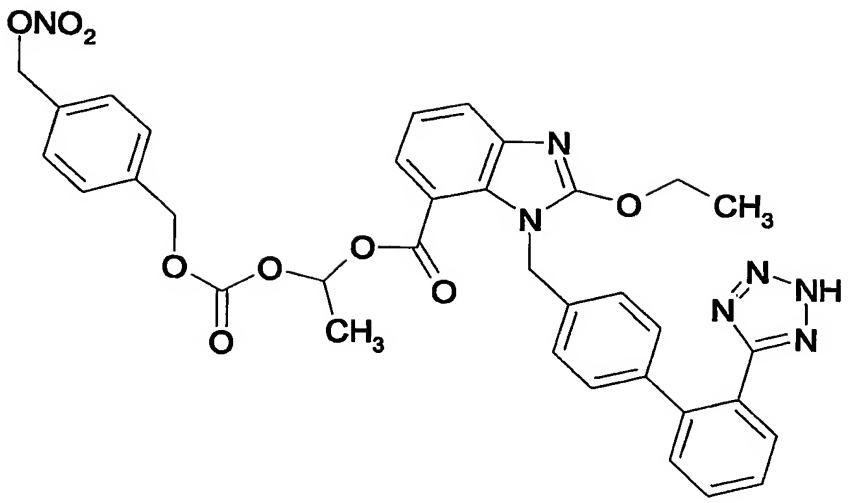

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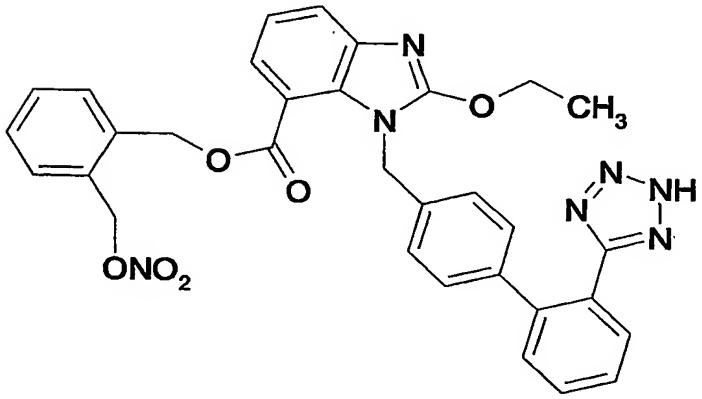

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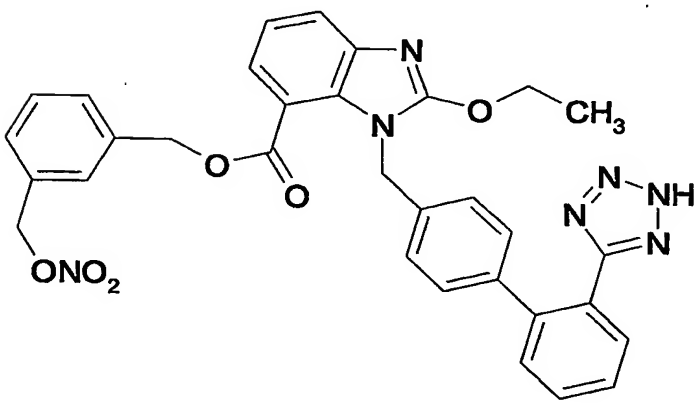

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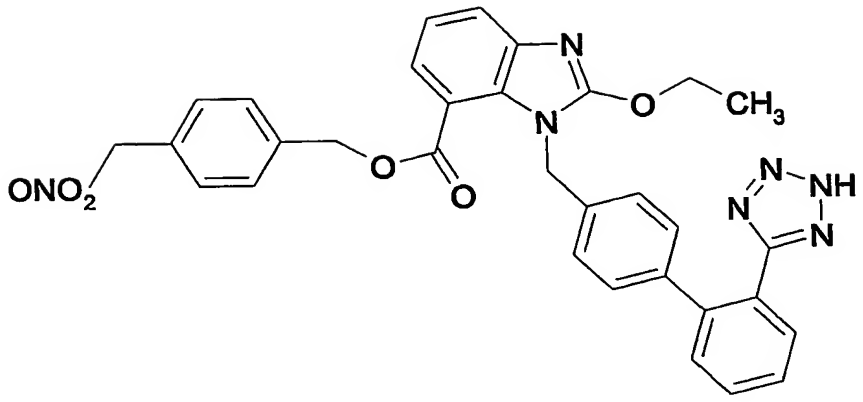

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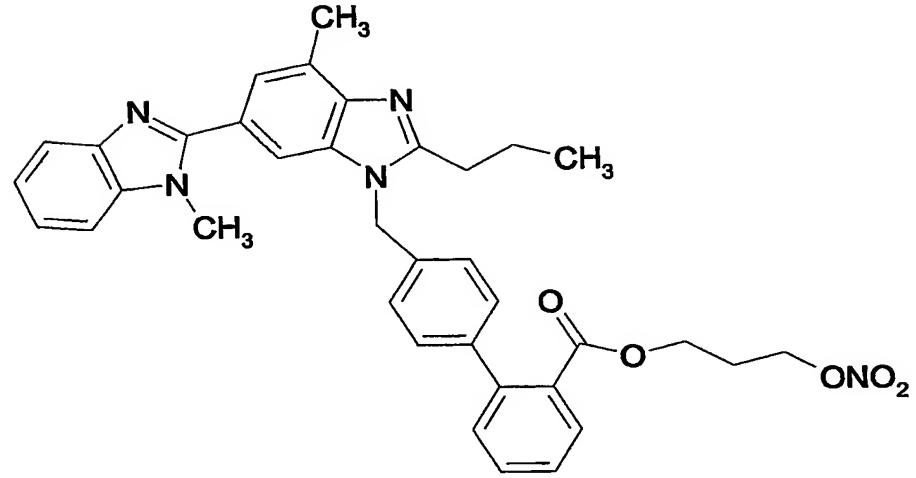

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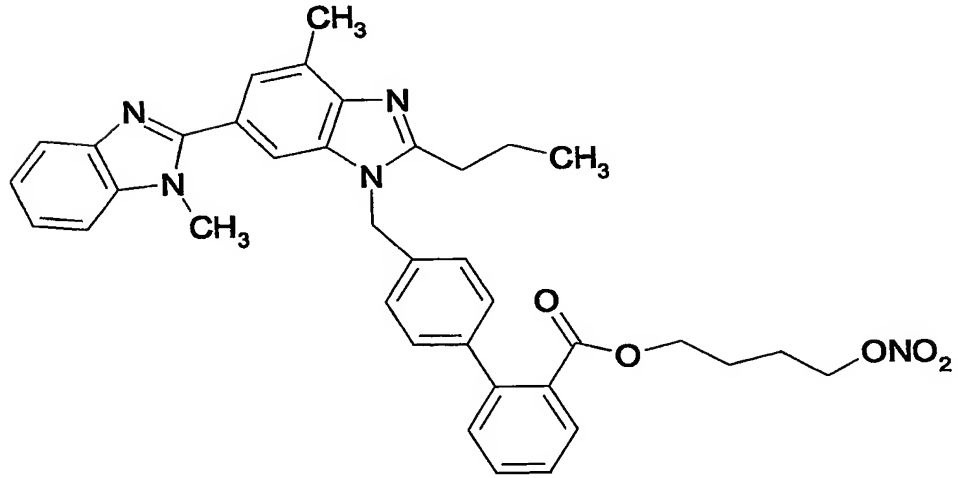

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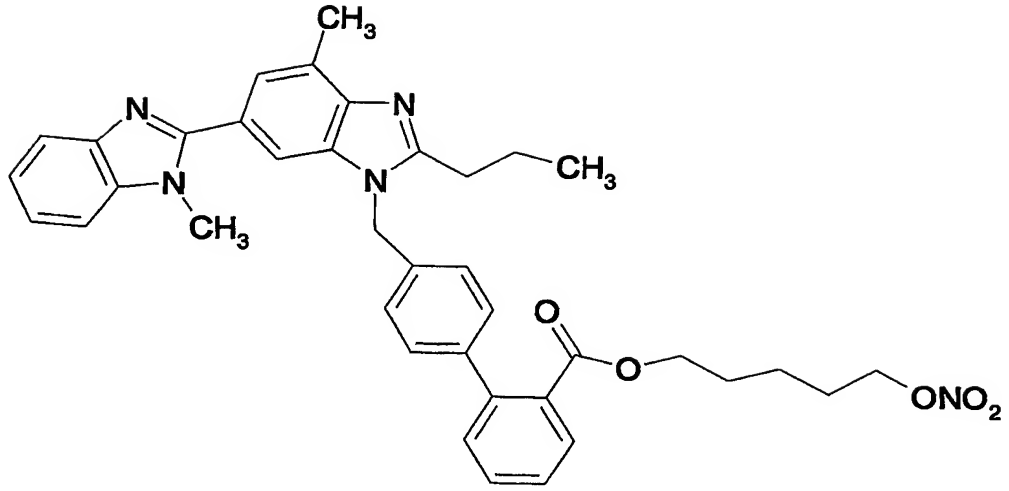

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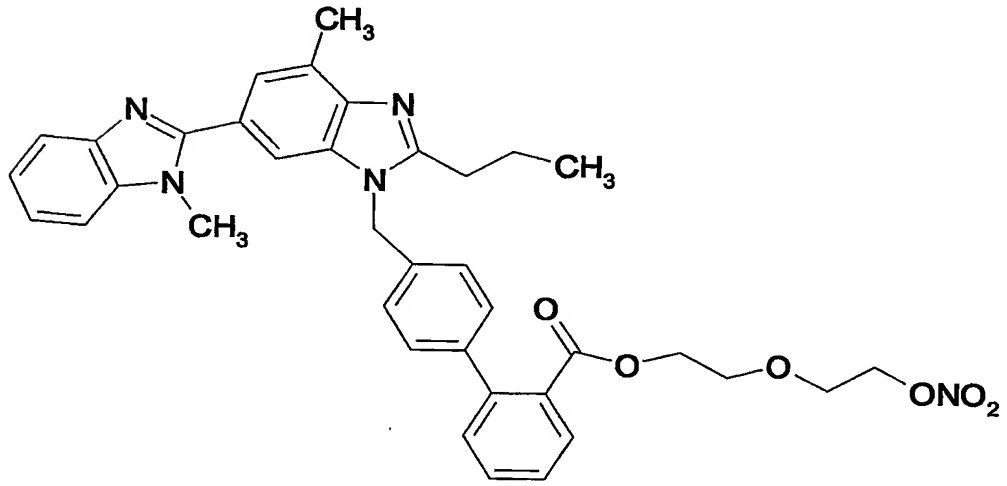

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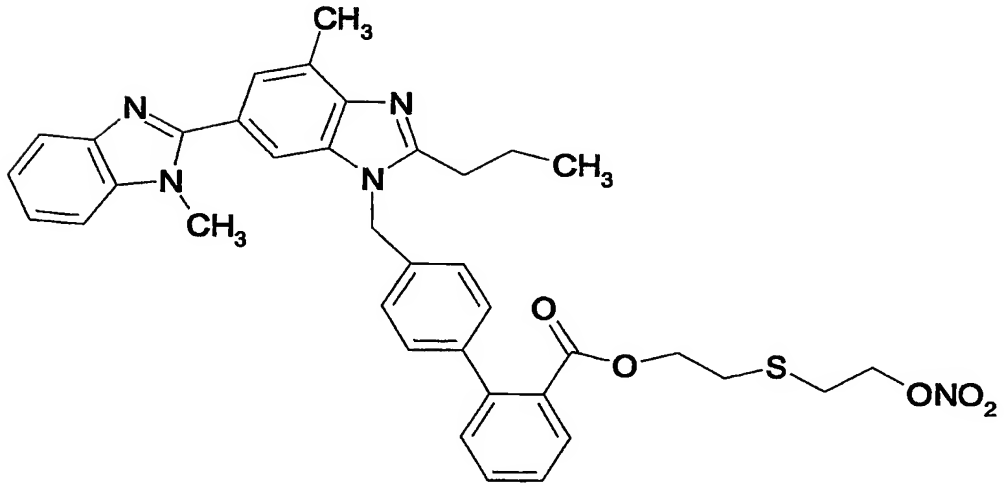

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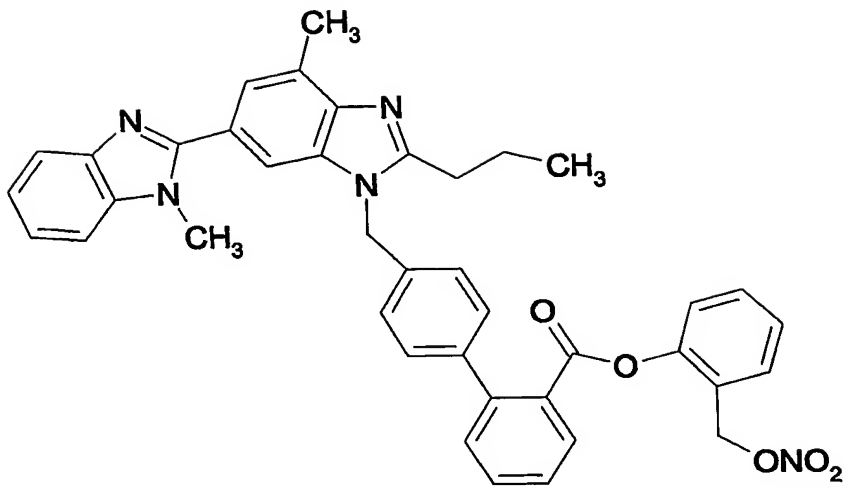

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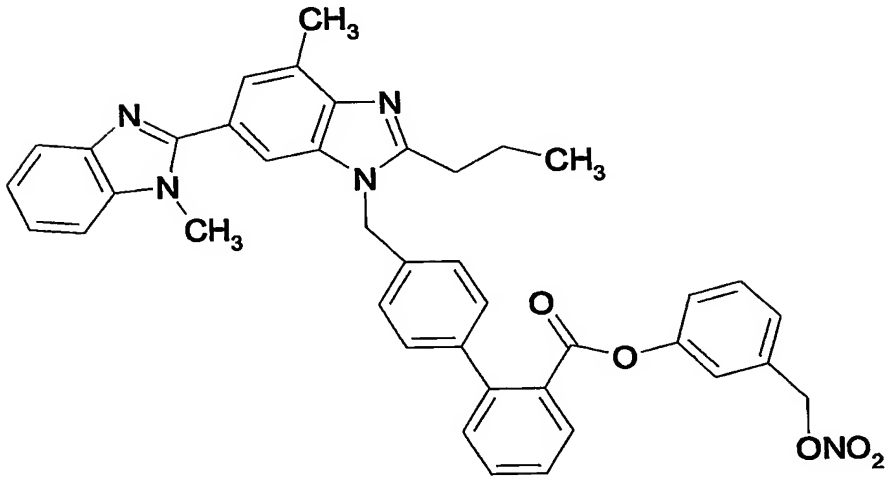

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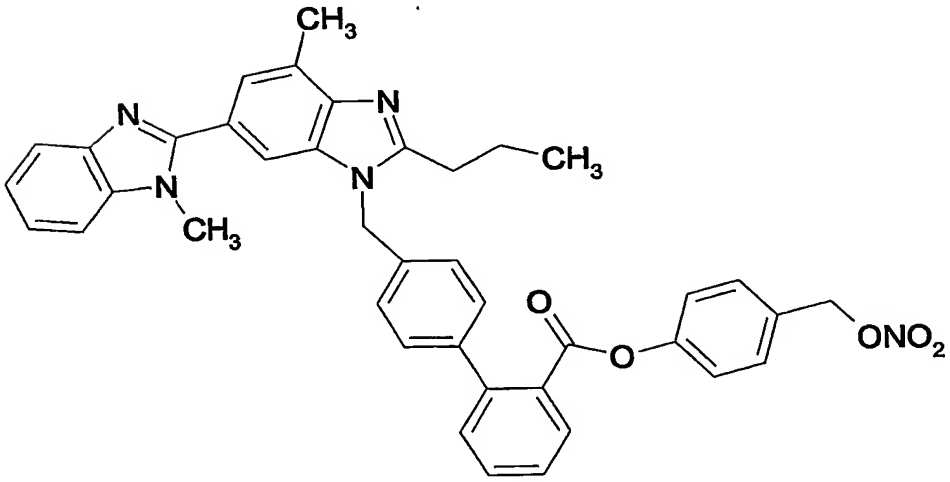

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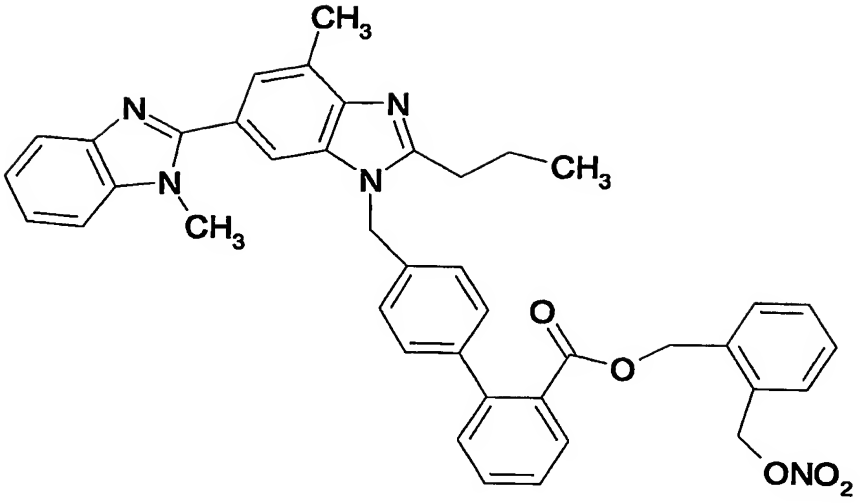

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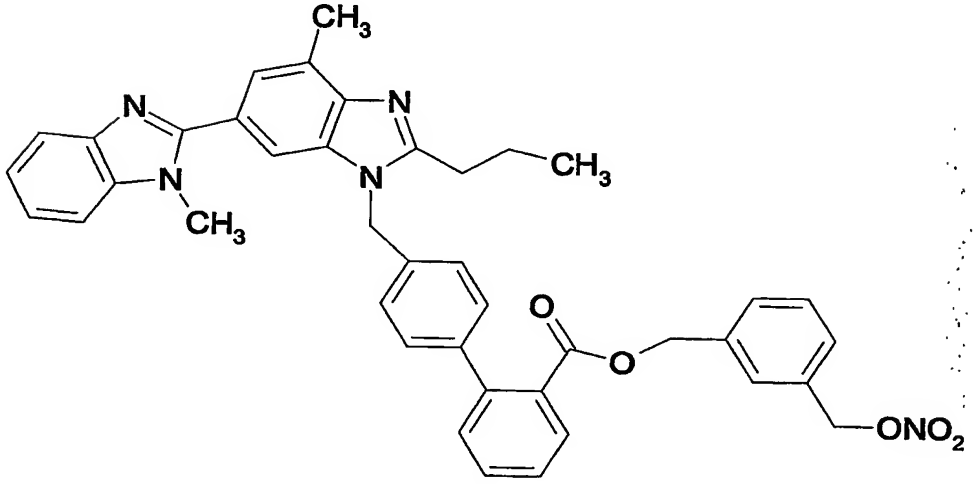

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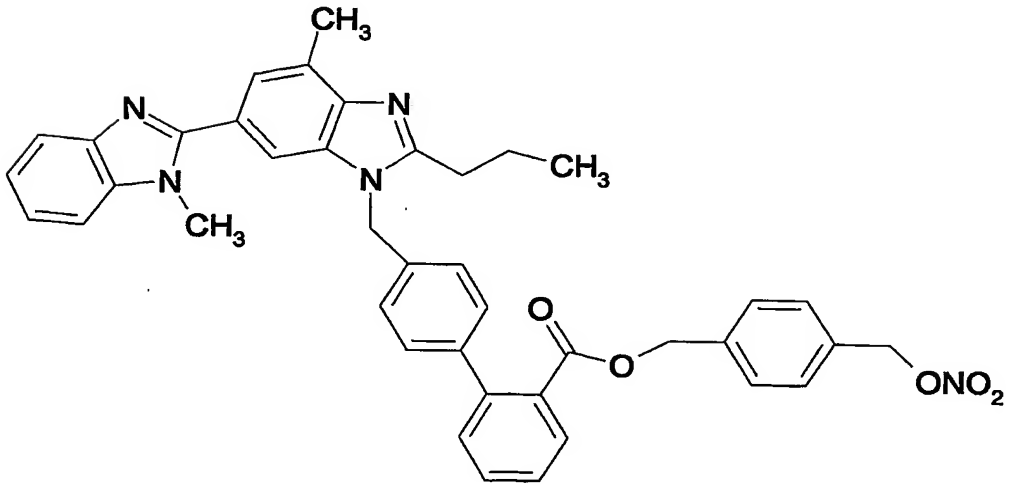

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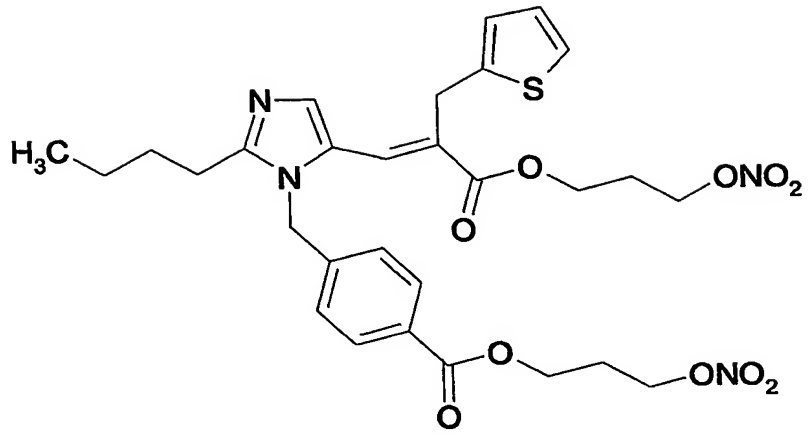

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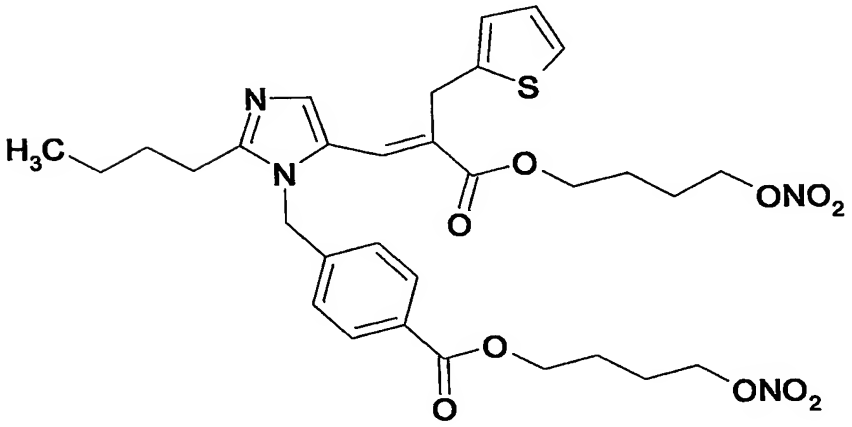

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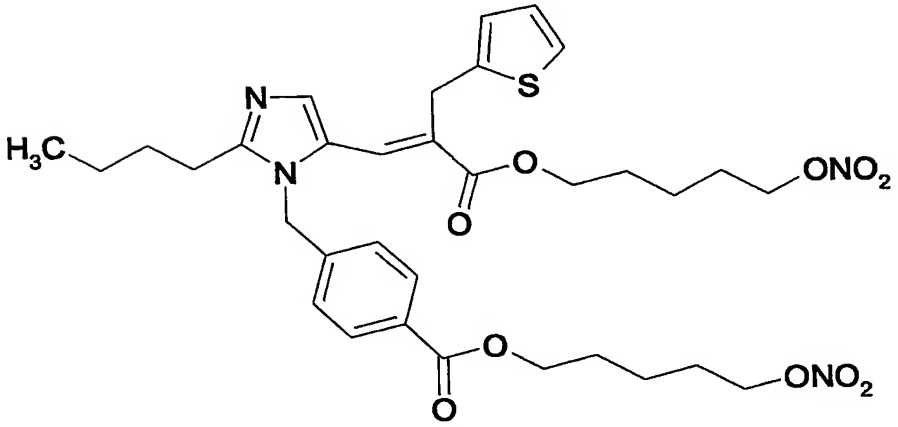

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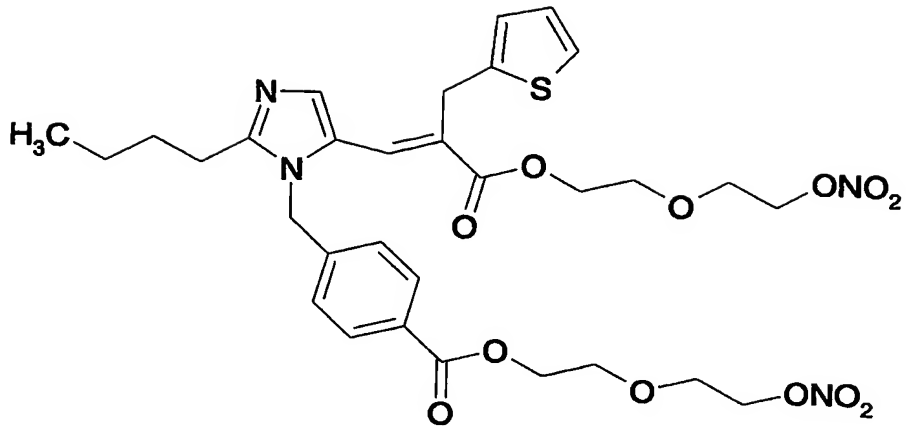

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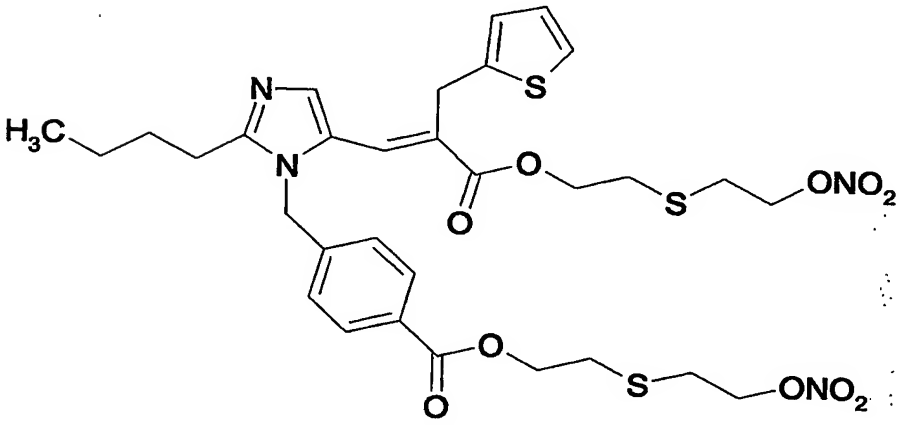

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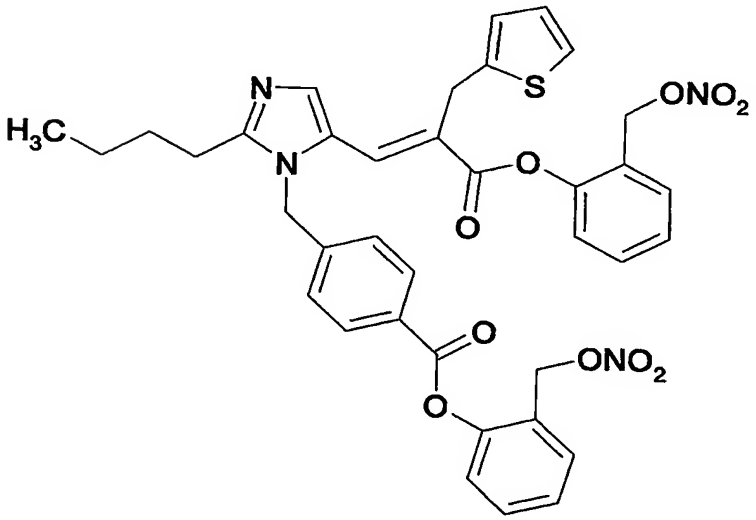

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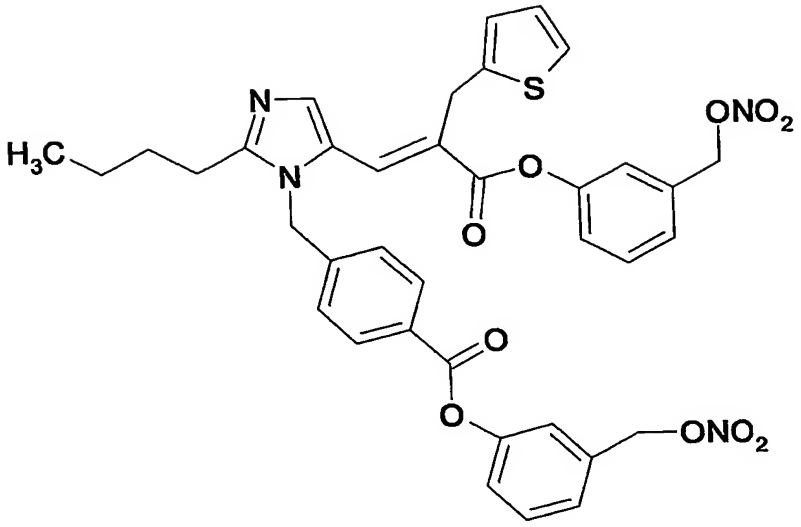

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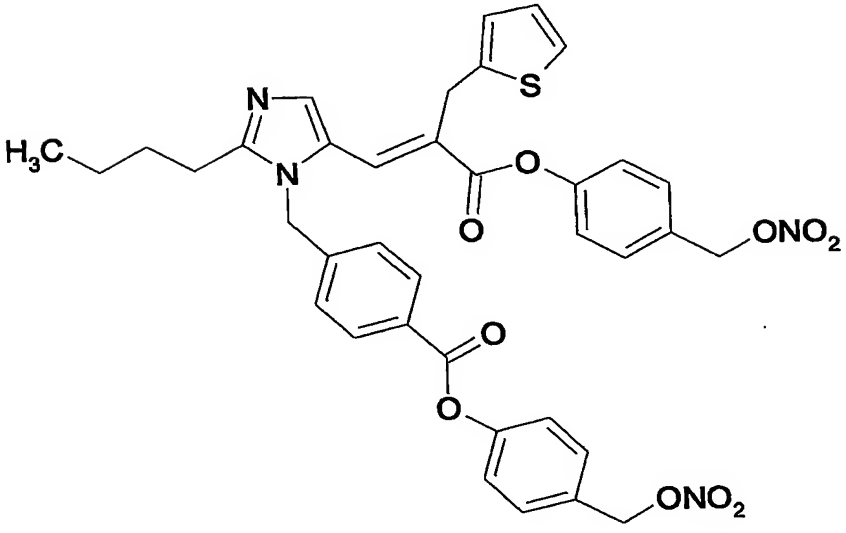

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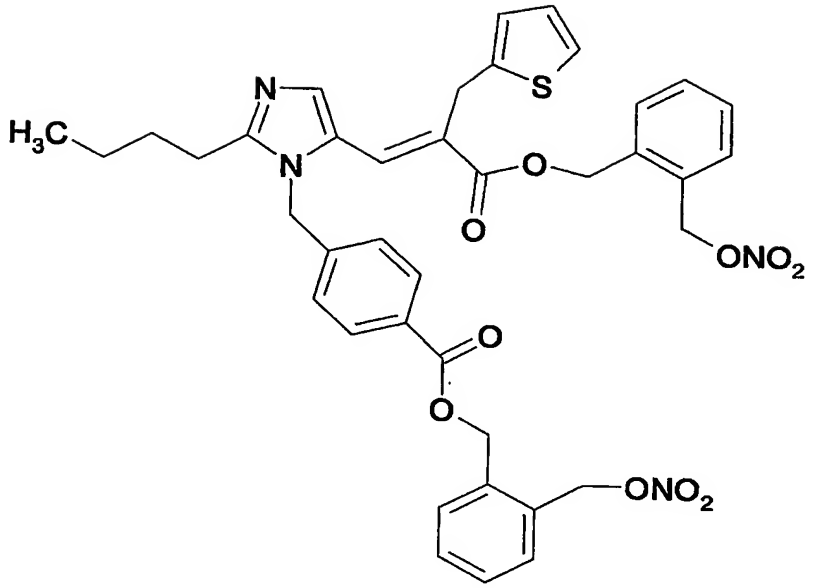

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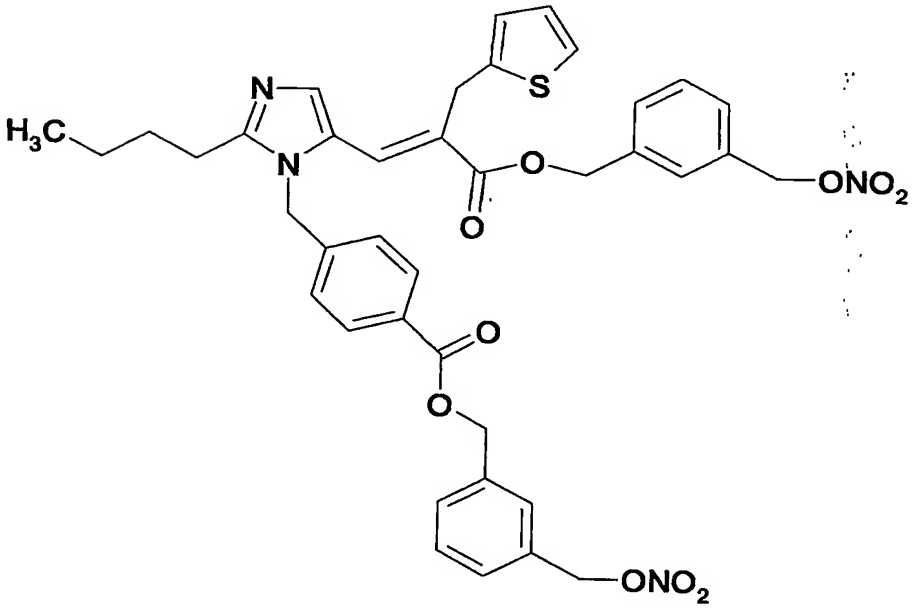

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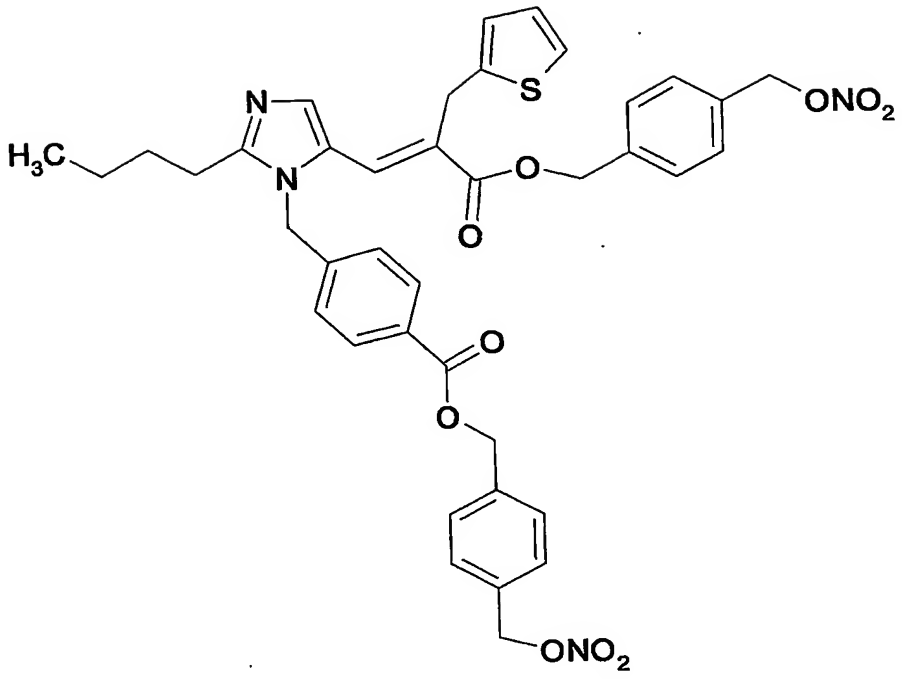

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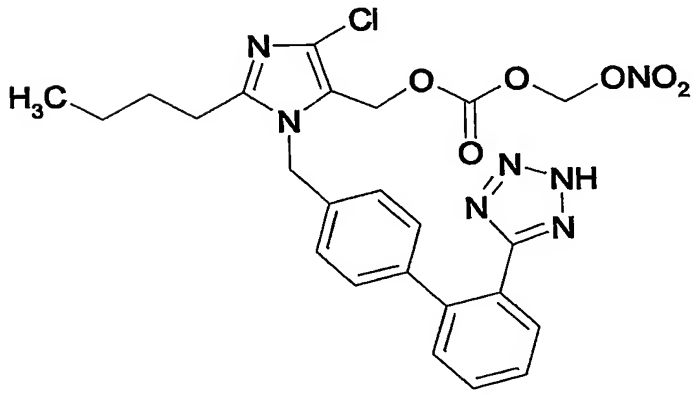

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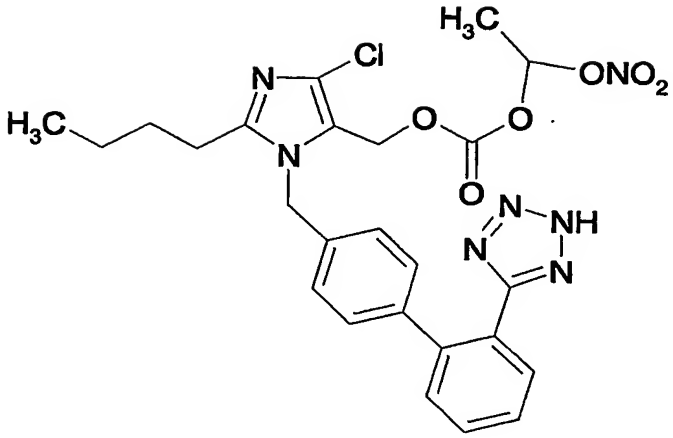

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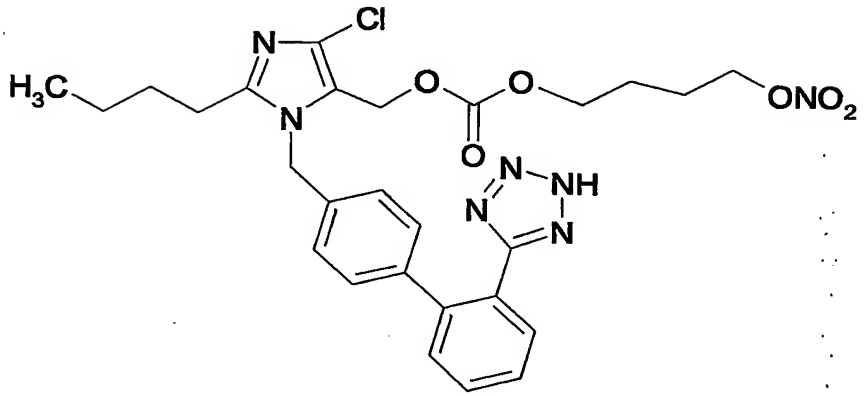

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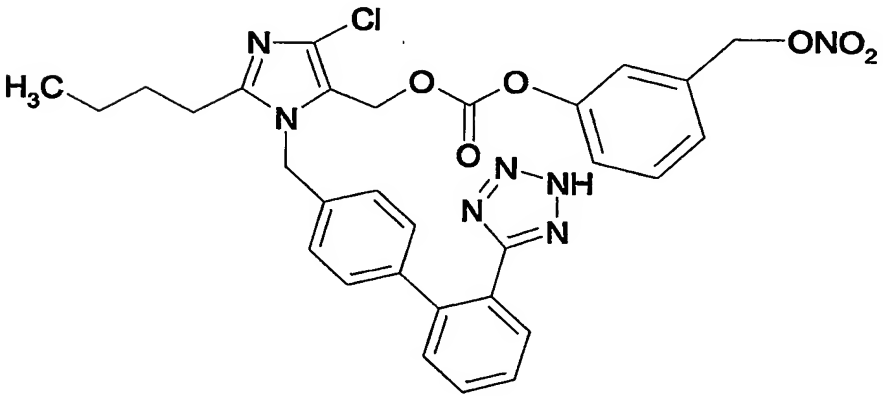

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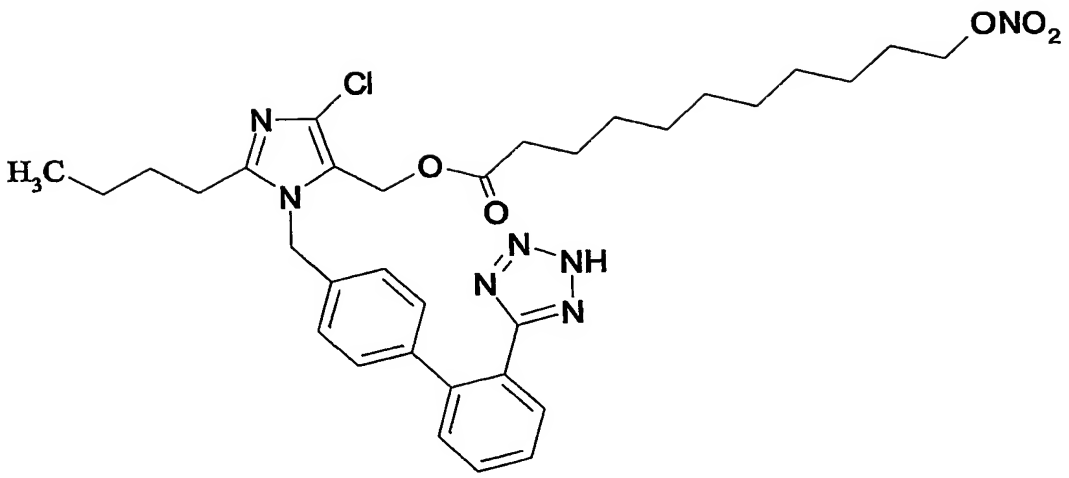

(68)

4. Use of a compound according to claims 1-3, for preparing a drug that can be employed in the treatment or prophylaxis of cardiovascular, renal and chronic liver diseases and inflammatory processes.

5. Use of a compound according to claim 4, for preparing a drug that can be employed in the treatment or prophylaxis of heart failure, myocardial infarction, ischemic stroke, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and liver fibrosis.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) or a salt or stereoisomer thereof according to claims 1-3.

7. A pharmaceutical composition according to claim 6 in a suitable form for the oral, parenteral, rectal, topic and transdermic administration, by inhalation spray or aerosol or iontophoresis devices.

8. Liquid or solid pharmaceutical composition for oral, parenteral, rectal, topic and transdermic administration or inhalation in the form of tablets, capsules and pills eventually with enteric coating, powders, granules, gels, emulsions, solutions, suspensions, syrups, elixir, injectable forms, suppositories, in transdermal patches or liposomes, containing a compound of formula (I) or a salt or stereoisomer thereof according to claims 1-3 and a pharmaceutically acceptable carrier.

ABSTRACT

Angiotensin II receptor blocker nitroderivatives of formula (I):

$$R-(Y-ONO_2)_s \quad (I)$$

having wider pharmacological activity and enhanced tolerability. They can be employed for treating cardiovascular, renal and chronic liver diseases and inflammatory processes.

PCT/EP2004/051550

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